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NOVEL IL-5 INHIBITING 6-AZAURACIL DERIVATIVES

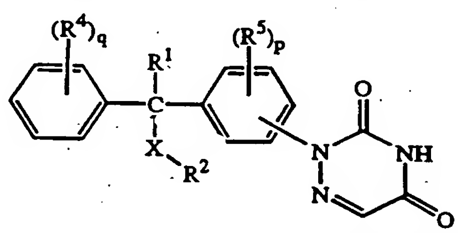
The present invention concerns novel IL-5 inhibiting 6-azauracil derivatives useful for treating eosinophil-dependent inflammatory diseases; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.

Eosinophil influx, leading to subsequent tissue damage, is an important pathogenic event in bronchial asthma and allergic diseases. The cytokine interleukin-5 (IL-5), produced mainly by T lymphocytes as a glycoprotein, induces the differentiation of eosinophils in bone marrow and, primes eosinophils for activation in peripheral blood and sustains their survival in tissues. As such, IL-5 plays a critical role in the process of eosinophilic inflammation. Hence, the possibility that inhibitors of IL-5 production would reduce the production, activation and/or survival of eosinophils provides a therapeutic approach to the treatment of bronchial asthma and allergic diseases such as, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and also other eosinophil-dependent inflammatory diseases.

Steroids, which strongly inhibit IL-5 production *in vitro*, have long been used as the only drugs with remarkable efficacy for bronchial asthma and atopic dermatitis, but they cause various serious adverse reactions such as diabetes, hypertension and cataracts. Therefore, it would be desirable to find non-steroidal compounds having the ability to inhibit IL-5 production in human T-cells and which have little or no adverse reactions.

US 4,631,278 discloses a-aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitriles and US 4,767,760 discloses 2-(substituted phenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-diones, all having anti-protozoal activity, in particular, anti-coccidial activity. EP 831,088 discloses 1,2,4-triazine-3,5-diones as anticoccidial agents. Unexpectedly, the 6-azauracil derivatives of the present invention prove to be potent inhibitors of the production of IL-5.

The present invention is concerned with the compounds of formula



(I)

the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically

isomeric forms thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

q represents an integer being 0, 1, 2, 3, 4 or 5;

X represents O, S, NR^3 or a direct bond;

R^1 represents hydrogen, hydroxy, halo, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{3-7}cycloalkyl, aryl, arylC_{1-6}alkyl, aminoC_{1-4}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl or mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkylamino;

R^2 represents aryl, Het^1, C_{3-7}cycloalkyl, C_{1-6}alkyl or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy, C_{1-6}alkylsulfonyloxy, C_{1-6}alkyloxycarbonyl, C_{3-7}cycloalkyl, aryl, aryloxy, arylthio, Het^1, Het^1oxy and Het^1thio; and if X is O, S or NR^3, then R^2 may also represent aminocarbonyl, aminothiocarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkylthiocarbonyl, arylcarbonyl or arylthiocarbonyl;

R^3 represents hydrogen or C_{1-4}alkyl;

each R^4 independently represents C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with Het^3, R^6 or NR^7R^8;

each R^5 independently represents C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with Het^3, R^6 or NR^7R^8;

each R^6 independently represents C_{1-6}alkylsulfonyl, aminosulfonyl, mono- or di-(C_{1-4}alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl, phenylC_{1-4}alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C_{1-4}alkyl-*N*-piperidinylaminosulfonyl;

each R^7 and each R^8 are independently selected from hydrogen, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, arylcarbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkyl-carbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, Het^3 and R^6;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, Het^3 and R^6;

each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo,

trihalomethyl, C_{1-4}alkyloxy, carboxyl, C_{1-4}alkyloxycarbonyl, trihaloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, $C(=O)NR^7R^8$, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, phthalimide-2-yl, Het^3 and $C(=O)Het^3$;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylamino-carbonyl, phenylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl and R^6;

aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, polyhaloC_{1-4}alkyl, NR^9R^{10}, R^6, phenyl, Het^3 and C_{1-4}alkyl substituted with NR^9R^{10};

Het^1 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl, imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11};

Het^2 represents a monocyclic heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl and triazinyl; wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4}alkyl optionally substituted with R^{11};

Het^3 represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two or three substituents each independently selected from C_{1-4}alkyl, C_{1-4}alkyloxy, carboxyl, C_{1-4}alkyloxycarbonyl, C_{1-4}alkylcarbonyl, phenylC_{1-4}alkyl, piperidinyl, $NR^{12}R^{13}$, R^6 and C_{1-4}alkyl substituted with R^6 or $NR^{12}R^{13}$.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; polyhaloC_{1-4}alkyl is defined as polyhalosubstituted C_{1-4}alkyl, in particular C_{1-4}alkyl substituted with 1 to 6 halogen atoms, more in particular difluoro- or trifluoromethyl; polyhaloC_{1-6}alkyl is defined as polyhalosubstituted C_{1-6}alkyl.

Het^1, Het^2 and Het^3 are meant to include all the possible isomeric forms of the heterocycles mentioned in the definition of Het^1, Het^2 or Het^3, for instance, pyrrolyl also includes *2H*-pyrrolyl; triazolyl includes 1,2,4-triazolyl and 1,3,4-triazolyl; oxadiazolyl includes 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl; thiadiazolyl includes 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl and 1,3,4-thiadiazolyl; pyranyl includes *2H*-pyranyl and *4H*-pyranyl.

The heterocycles represented by Het^1, Het^2 and Het^3 may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is imidazolyl, it may be a 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is thiazolyl, it may be 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl; when it is benzthiazolyl, it may be 2-benzthiazolyl, 4-benzthiazolyl, 5-benzthiazolyl, 6-benzthiazolyl and 7-benzthiazolyl.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxy-acetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by

treatment with alkali into the free base form.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.
The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide. For example, one or more nitrogen atoms of any of the heterocycles in the definition of Het^1, Het^2 and Het^3 may be *N*-oxidized.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For example, a hydroxy substituted triazine moiety may also exist as the corresponding triazinone moiety; a hydroxy substituted pyrimidine moiety may also exist as the corresponding pyrimidinone moiety.

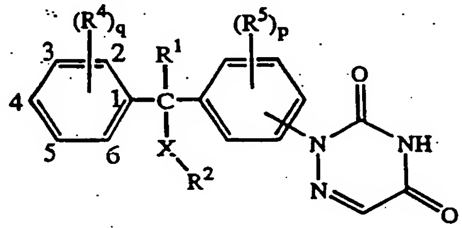
The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) can exist. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration, used herein in accordance with Chemical Abstracts nomenclature. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

The compounds of formula (I) and some of the intermediates in the present invention contain one or more asymmetric carbon atoms. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the

scope of the present invention.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

The numbering of the phenyl ring bearing substituent R^4 is given hereinbelow and is used herein as such when indicating the position of the R^4 substituents on said phenyl ring, unless otherwise indicated.



The carbon atom bearing the two phenyl rings and the R^1 and $-X-R^2$ substituents will be referred herein as the central carbon atom.

A special group of compounds are those compounds of formula (I) wherein R^1 represents hydrogen, hydroxy, halo, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{3-7}cycloalkyl, aryl or arylC_{1-6}alkyl; R^2 represents aryl; Het^1; C_{3-7}cycloalkyl; C_{1-6}alkyl or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, C_{3-7}cycloalkyl, aryl and Het^1; and if X is NR^3, then R^2 may also represent C_{1-4}alkylcarbonyl or arylcarbonyl; each R^4 independently represents halo, polyhaloC_{1-6}alkyl, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyloxy, mercapto, C_{1-6}alkylthio, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl, polyhaloC_{1-6}alkylsulfonyl, aryl, cyano, nitro, amino, mono- and di(C_{1-6}alkyl)amino or (C_{1-6}alkylcarbonyl)amino; each R^5 independently represents halo, polyhaloC_{1-6}alkyl, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyloxy, mercapto, C_{1-6}alkylthio, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl, polyhaloC_{1-6}alkylsulfonyl, aryl, cyano, nitro, amino, mono- and di(C_{1-6}alkyl)amino or (C_{1-6}alkylcarbonyl)amino; aryl represents phenyl or phenyl substituted with one, two or three substituents selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, polyhaloC_{1-4}alkyl, amino, mono- or di(C_{1-4}alkyl)amino and phenyl; Het^1 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, piperidinyl,

piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzthiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl and thiazolopyridinyl; said heterocycles each independently may be substituted with one, or where possible, two or three R^{11} substituents, each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, C_{1-4}alkyl, C_{1-4}alkyloxy, amino, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminocarbonyl, mono- or di(aryl)amino, halo, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, aryl, furanyl, thienyl, pyridinyl, piperidinyl, C_{1-4}alkyl-carbonylpiperidinyl and C_{1-4}alkyl substituted with C_{1-4}alkyloxy, aryl, hydroxy, piperidinyl, amino, mono- or di(C_{1-4}alkyl)amino or C_{3-7}cycloalkyl.

An interesting group of compounds are those compounds of formula (I) wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative to the central carbon atom; preferably in the para position.

Suitably, p is 0, 1 or 2; preferably 1 or 2.
Suitably, q is 0, 1 or 2; preferably 1 or 2.
Suitably, R^1 represents hydrogen, hydroxy, halo, amino, C_{1-6}alkyl, C_{1-6}alkyloxy or mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkylamino; in particular, hydrogen, methyl and hydroxy.
Suitably, R^2 represents aryl, Het^1, C_{3-7}cycloalkyl, C_{1-6}alkyl or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)-amino, C_{1-6}alkyloxy, C_{1-6}alkylsulfonyloxy, C_{1-6}alkyloxycarbonyl, aryl, Het^1 and Het^1thio; and if X is NR^3, then R^2 may also represent arylcarbonyl.
Suitably, R^3 represents hydrogen or methyl.
Suitably, each R^4 independently represents C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl or C_{1-6}alkyloxy.
Suitably, each R^5 independently represents C_{1-6}alkyl, halo or C_{1-6}alkyloxy.
Suitably, each R^6 independently represents C_{1-6}alkylsulfonyl, aminosulfonyl or phenylC_{1-4}alkylsulfonyl.
Suitably, each R^7 and each R^8 are independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, Het^3 and R^6.
Suitably, R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxy

carbonylcarbonyl, Het^3aminothiocarbonyl and R^6.
Suitably, R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4}alkyl.
Suitably, Het^1 represents a heterocycle selected from imidazolyl, triazolyl, furanyl, oxazolyl, thiazolyl, thiazolinyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, piperidinyl, piperazinyl, triazinyl, benzothiazolyl, benzoxazolyl, purinyl, 1*H*-pyrazolo-[3,4-d]pyrimidinyl, benzimidazolyl, thiazolopyridinyl, oxazolopyridinyl, imidazo-[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11}.
Suitably, Het^2 represents furanyl, thienyl or pyridinyl; wherein said monocyclic heterocycles each independently may optionally be substituted with C_{1-4}alkyl.
Suitably, Het^3 represents pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two or three substituents each independently selected from C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl, C_{1-4}alkylcarbonyl, phenylC_{1-4}alkyl, piperidinyl, $NR^{12}R^{13}$ and C_{1-4}alkyl substituted with $NR^{12}R^{13}$.

Particular compounds are those compounds of formula (I) wherein R^4 and R^5 each independently are halo, polyhaloC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy or aryl, more in particular, chloro or trifluoromethyl.

Other particular compounds are those compounds of formula (I) wherein R^2 represents aryl, Het^1, C_{3-7}cycloalkyl or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy, C_{1-6}alkylsulfonyloxy, C_{1-6}alkyloxycarbonyl, C_{3-7}cycloalkyl, aryl, aryloxy, arylthio, Het^1, Het^1oxy and Het^1thio; and if X is O, S or NR^3, then R^2 may also represent aminocarbonyl, aminothiocarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkylthiocarbonyl, arylcarbonyl or arylthiocarbonyl; more in particular R^2 is oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11}.

Yet other particular compounds are those compounds of formula (I) wherein X is O, S, NH or a direct bond, more preferably S or a direct bond, most preferably a direct bond.

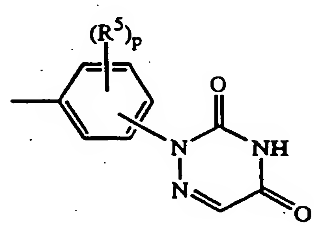
Preferred compounds are those compounds of formula (I) wherein q is 1 or 2 and one R^4 substituent, preferably chloro, is in the 4 position.

Other preferred compounds are those compounds of formula (I) wherein p is 1 or 2 and the one or two R^5 substituents, preferably chloro, are in the ortho position relative to the central carbon atom.

More preferred compounds are those compounds of formula (I) wherein the 6-azauracil moiety is in the para position relative to the central carbon atom; p is 2 and both R^5 substituent are chloro positioned ortho relative to the central carbon atom; q is 1 and R^4 is chloro positioned in the 4 position.

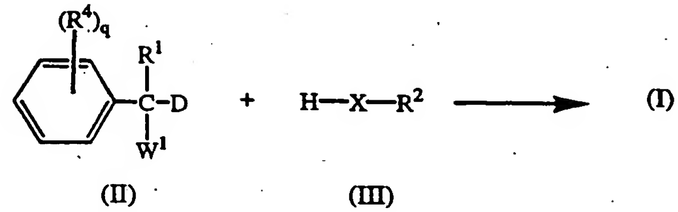
Most preferred compounds include
2-[3,5-dichloro-4-[(4-chlorophenyl)(2-pyrimidinylthio)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4 *H*)-dione;
2-[3,5-dichloro-4-[(4-chlorophenyl)[2-(4-pyridinyl)-4-thiazolyl]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione monohydrochloride.monohydrate;
2-[3,5-dichloro-4-[(4-chlorophenyl)(5-phenyl-1,3,4-oxadizol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[(4-chlorophenyl)[4-(2-chlorophenyl)-2-thiazolyl]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[(4-chlorophenyl)[4-(3-fluorophenyl)-2-thiazolyl]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[(4-chlorophenyl)(2-pyridinylthio)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione; the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof.

In order to simplify the structural representation of the compounds of formula (I), the group



will hereinafter be represented by the symbol D.

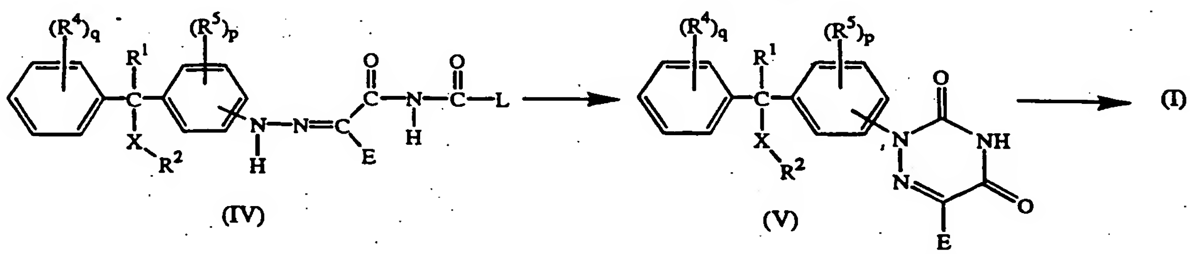
Compounds of formula (I) can generally be prepared by reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group such as, for example, a halogen atom, with an appropriate reagent of formula (III).



Said reaction may be performed in a reaction-inert solvent such as, for example, acetonitrile, *N,N*-dimethylformamide, acetic acid, tetrahydrofuran, ethanol or a mixture thereof. Alternatively, in case the reagent of formula (III) acts as a solvent, no additional reaction-inert solvent is required. The reaction is optionally carried out in the presence of a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium bicarbonate, sodiumethanolate and the like. Convenient reaction temperatures range between - 70°C and reflux temperature.

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

Alternatively, compounds of formula (I) may generally be prepared by cyclizing an intermediate of formula (IV) wherein L is a suitable leaving group such as, for example, C_{1-6}alkyloxy or halo, and E represents an appropriate electron attracting group such as, for example, an ester, an amide, a cyanide, C_{1-6}alkylsulfonyloxy and the like groups; and eliminating the group E of the thus obtained triazinedione of formula (V). Said reaction procedure is analogous to the one described in EP-A-0,170,316.

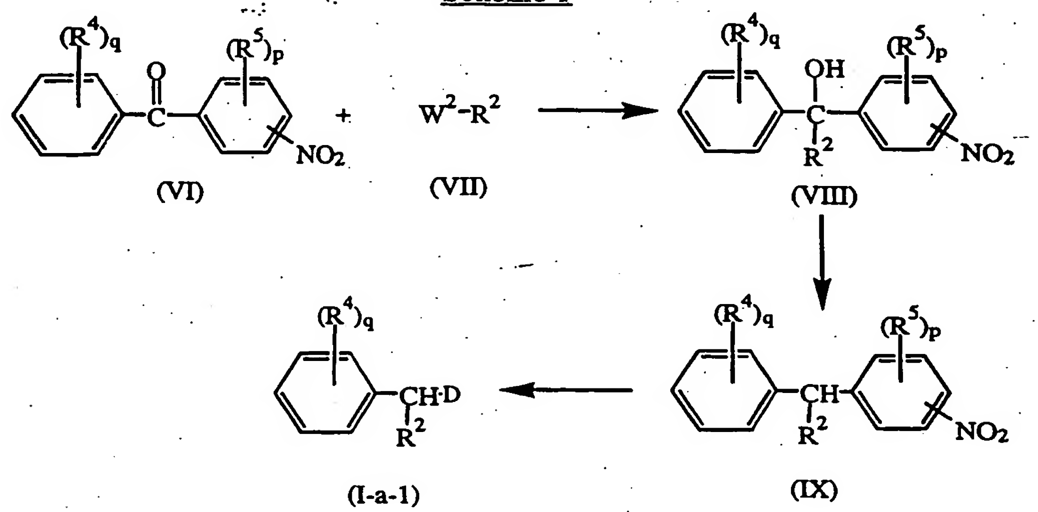


Some of the compounds and intermediates of the present invention can be prepared according to or analogous to the procedures described in EP-A-0,170,316 and EP-A-0,232,932.

For instance, scheme 1 depicts a reaction pathway for the preparation of compounds of formula (I) wherein R^1 is hydrogen and X is a direct bond, said compounds being represented by formula (I-a-1). A ketone of formula (VI) can be reacted with a reagent of formula (VII) wherein W^2 is a suitable leaving group such as, for example, a halogen,

in a reaction-inert solvent such as, for example, tetrahydrofuran, diethylether, and in the presence of a suitable base such as, for example, butyl lithium, thus forming an intermediate of formula (VIII). The hydroxy group of the intermediates of formula (VIII) may be eliminated by using a suitable reagent such as for example, formamide in acetic acid or triethylsilane in trifluoroacetic acid, thus obtaining an intermediate of formula (IX) of which the nitro group may subsequently be reduced to an amino group which in turn may then be converted to the 6-azauracil group as described in EP-A-0,170,316, thus obtaining compounds of formula (I-a-1).

Scheme 1



In addition to the reaction procedure shown in scheme 1, other compounds of formula (I) wherein X is a direct bond may be prepared starting from a ketone of formula (X) (Scheme 2). Reacting said ketone of formula (X) with an intermediate of formula (III) wherein X is a direct bond, said intermediates being represented by formula (III-a), results in a compound of formula (I) wherein R^1 is hydroxy and X is a direct bond, said compounds being represented by formula (I-a-2). Said reaction may be performed in a reaction-inert solvent such as, for example, tetrahydrofuran, diethylether, diisopropylacetamide or a mixture thereof, in the presence of a base such as, for example, butyl lithium, and optionally in the presence of chlorotriethylsilane. Alternatively, intermediate of formula (III-a) may first be transformed into a Grignard reagent, which may then be reacted with the ketone of formula (X). Said compounds of formula (I-a-2) may further be converted to compounds of formula (I) wherein R^1 is a C_{1-6}alkyloxy group represented by formula (I-a-3) using art-known group transformation reactions. The compounds of formula (I-a-2) may also be converted to compounds of formula (I) wherein R^1 is halo, said compounds being represented by formula (I-a-4). A convenient procedure is converting the hydroxy group to a chlorine atom using a suitable reagent

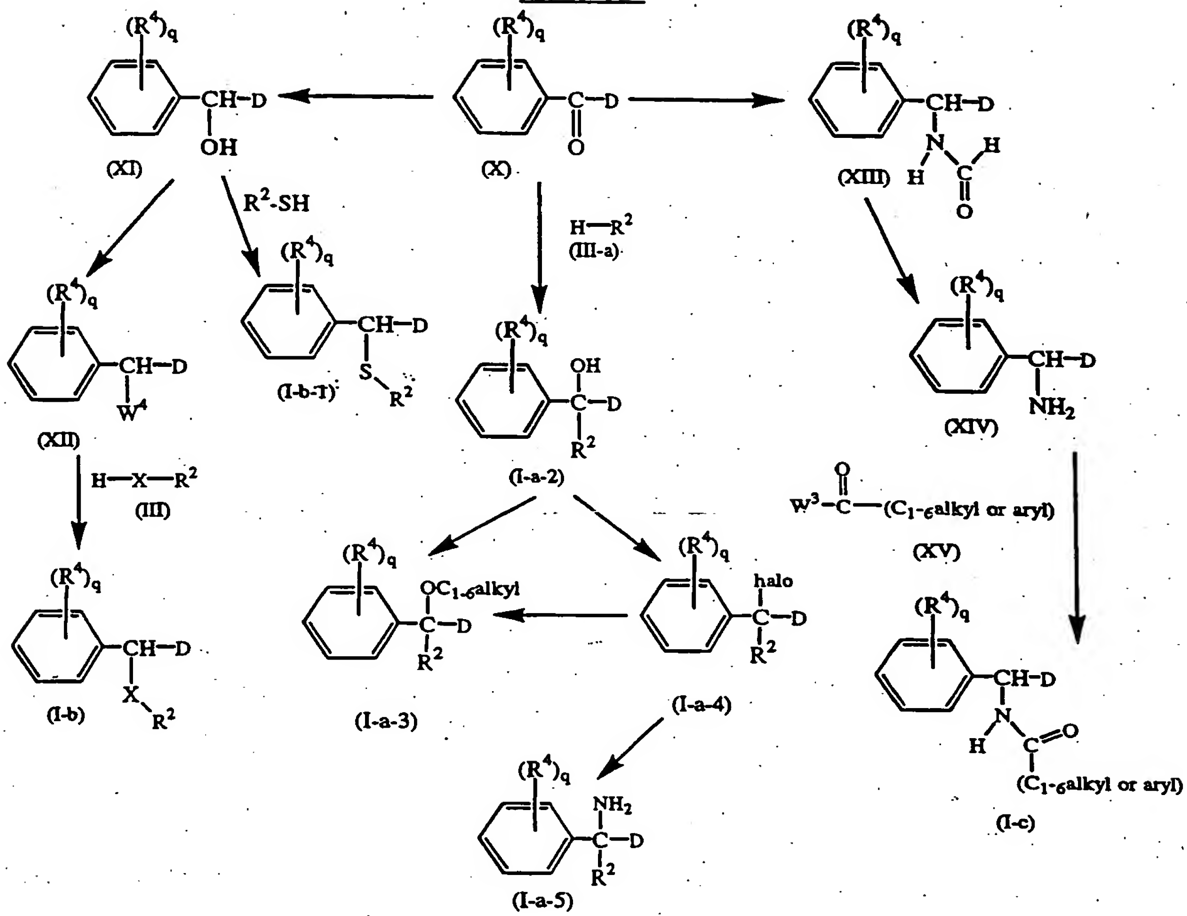
such as, for example, thionyl chloride. Said compounds of formula (I-a-4) may further be converted to compounds of formula (I) wherein R^1 is amino, said compounds being represented by formula (I-a-5), using ammonia or a functional derivative thereof, in a reaction-inert solvent such as, for example, tetrahydrofuran; or may be converted to compounds of formula (I-a-3) using art-known group transformation reactions.

Reducing the ketone of formula (X) to its corresponding hydroxy derivative of formula (XI) using a suitable reducing agent such as, for example, sodiumborohydride in a reaction-inert solvent such as for example, water, an alcohol, tetrahydrofuran or a mixture thereof; subsequently converting said hydroxy group to a suitable leaving group W^4 being for example a halogen, thus obtaining an intermediate of formula (XII), and finally reacting said intermediate of formula (XII) with an intermediate of formula (III) in a suitable solvent such as, for example, tetrahydrofuran, *N,N*-dimethylformamide, acetonitrile, acetic acid, ethanol or a mixture thereof, and optionally in the presence of a suitable base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene or sodiumbicarbonate, will result in a compound of formula (I) wherein R^1 is hydrogen, said compounds being represented by formula (I-b).

Alternatively, intermediates of formula (XI) can be directly transformed to compounds of formula (I-b) wherein X is S, said compounds being represented by formula (I-b-1), using a suitable mercapto containing reagent of formula R^2-SH in a suitable reaction solvent such as, for example, trifluoroacetic acid, methanesulfonic acid, trifluoromethanesulfonic acid or the like.

Also starting from a ketone of formula (X), compounds of formula (I) may be prepared wherein R^1 is hydrogen and -X-R^2 is -NH-C(=O)-(aryl or C_{1-6}alkyl), said compounds being represented by formula (I-c). To that effect, a ketone of formula (X) is reacted with formamide in formic acid or a functional derivative thereof, at elevated temperatures. The resulting intermediate of formula (XIII) is hydrolysed to the corresponding amine of formula (XIV), which may then be further reacted with an intermediate of formula (XV) wherein W^3 is a suitable leaving group, in the presence of a suitable base, such as, for example pyridine, optionally in the presence of a reaction-inert solvent such as, for example, dichloromethane.

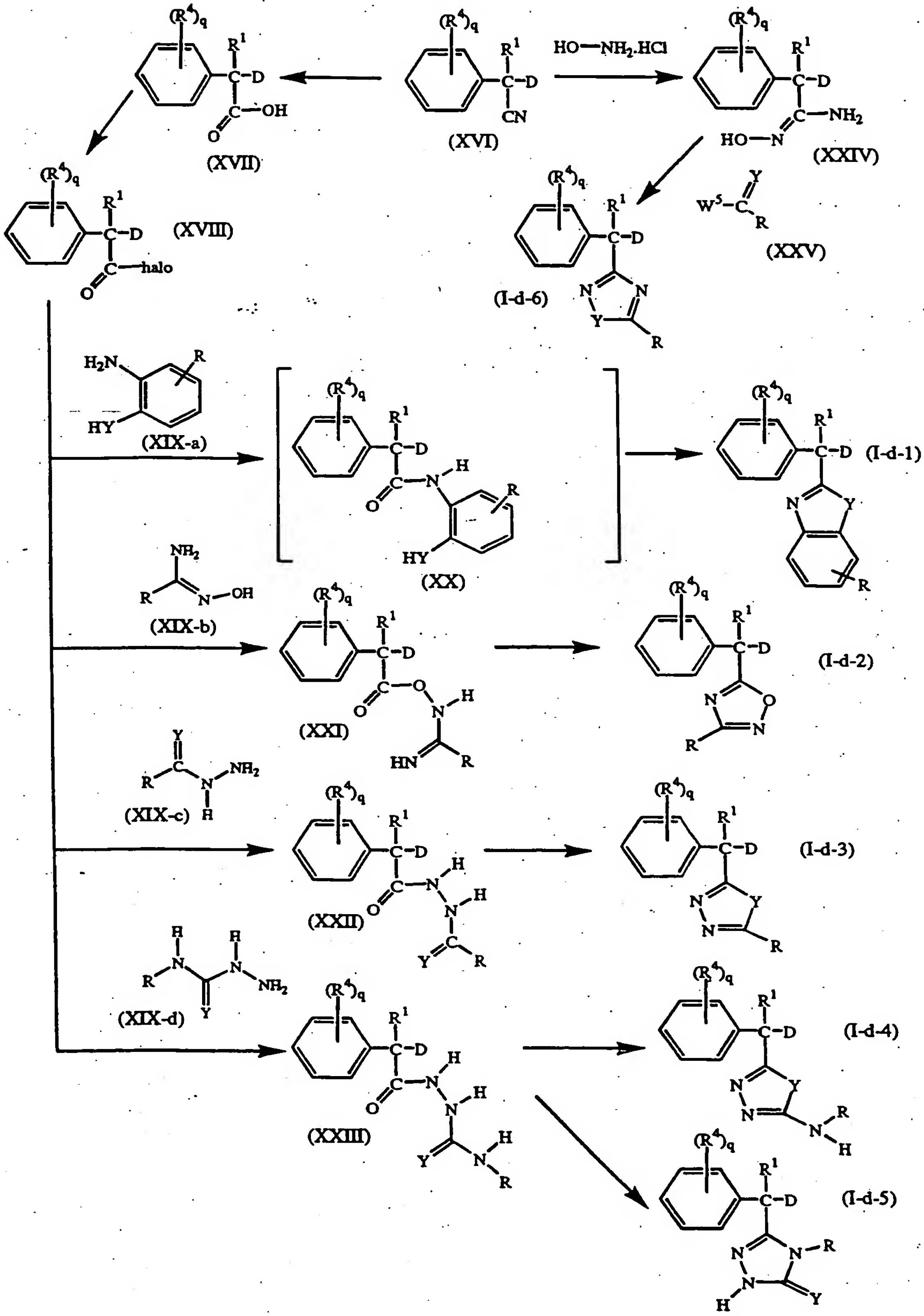
Scheme 2



Compounds of formula (I) wherein X is a direct bond and R^2 is a heterocycle, said compounds being generally represented by formula (I-d), can conveniently be prepared by cyclization of the appropriate intermediate. Both intramolecular and intermolecular cyclization procedures are feasable and scheme 3 lists several examples.

Starting point is the conversion of the cyano group of an intermediate of formula (XVI) to a carboxyl group thus forming intermediates of formula (XVII) using art-known techniques such as, for example, using a combination of sulfuric- and acetic acid in water, which in turn may be further reacted to acyl halides of formula (XVIII), for instance, the acyl chloride derivative may be prepared using thionyl chloride.

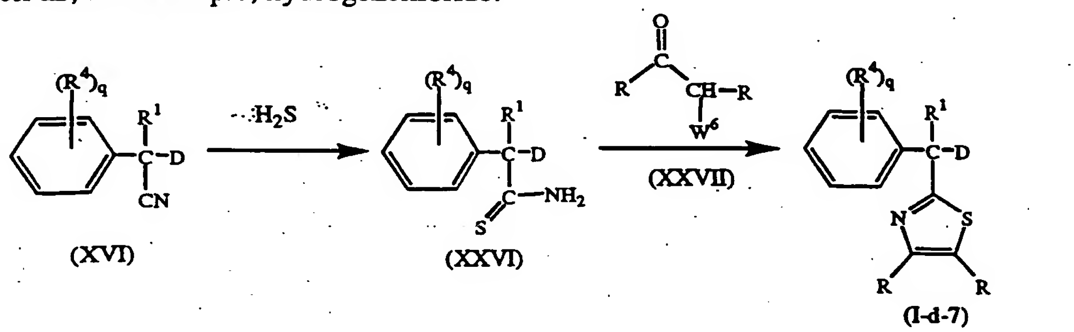
Scheme 3


(R⁴)q
R1
C-D
C-OH
O
(XVII)
CN
(XVI)
HO—NH2.HCl
C-NH2
HO-N
(XXIV)
(XVIII)
halo
W5-C
Y
R
(XXV)
(I-d-6)
H2N
HY
(XIX-a)
(XX)
(I-d-1)
NH2
N-OH
(XIX-b)
(XXI)
HN
(I-d-2)
(XIX-c)
(XXII)
(I-d-3)
(XIX-d)
(XXIII)
(I-d-4)
(I-d-5)

The intermediate of formula (XVIII) may be reacted with an intermediate of formula (XIX-a) wherein Y is O, S or NR^3, to form an intermediate of formula (XX) in the presence of a base such as, for example, pyridine. Said intermediate of formula (XX) may further be cyclized to a compound of formula (I) wherein -X-R^2 is an optionally substituted benzothiazole or benzoxazole, said compounds being represented by formula (I-d-1), in the presence of a suitable solvent such as, for example, acetic acid, at an elevated temperature, preferably at reflux temperature. It may be convenient to prepare compounds of formula (I-d-1) without isolating intermediates of formula (XX). Analogously, an intermediate of formula (XVIII) may be reacted with an intermediate of formula (XIX-b) to form an intermediate of formula (XXI) which is cyclized to a compound of formula (I) wherein -X-R^2 is an optionally 3-substituted 1,2,4-oxadiazole, said compounds being represented by formula (I-d-2), in a reaction-inert solvent such as, for example, toluene, at an elevated temperature, preferably at reflux temperature. Also analogously, an intermediate of formula (XVIII) may be reacted with an intermediate of formula (XIX-c) wherein Y is O, S or NR^3, to form an intermediate of formula (XXII) which is cyclized to a compound of formula (I) wherein -X-R^2 is an optionally substituted 1,2,4-triazole, 1,3,4-thiadiazole or 1,3,4-oxadiazole, said compounds being represented by formula (I-d-3), in a suitable solvent such as, for example, phosphorousoxychloride. Also analogously, an intermediate of formula (XVIII) may be reacted with an intermediate of formula (XIX-d) wherein Y is O, S or NR^3, to form an intermediate of formula (XXIII) which is cyclized to a compound of formula (I) wherein -X-R^2 is an optionally amino substituted 1,2,4-triazole, 1,3,4-thiadiazole or 1,3,4-oxadiazole, said compounds being represented by formula (I-d-4) in a reaction-inert solvent such as, for example; toluene, and in the presence of an acid; or, which is cyclized to a compound of formula (I) wherein -X-R^2 is a disubstituted 1,3,4-triazole, said compounds being represented by formula (I-d-5). The nitrile derivative of formula (XVI) may also be reacted with hydroxylamine hydrochloride or a functional derivative thereof, thus forming an intermediate of formula (XXIV) which may be reacted with an intermediate of formula (XXV) to form a compound of formula (I) wherein -X-R^2 is an optionally 5-substituted 1,2,4-triazole, 1,2,4-thiadiazole or 1,2,4-oxadiazole, said compounds being represented by formula (I-d-6), in a reaction-inert solvent such as, for example, methanol, butanol or a mixture thereof, and in the presence of a base such as, for example, sodium methanolate.

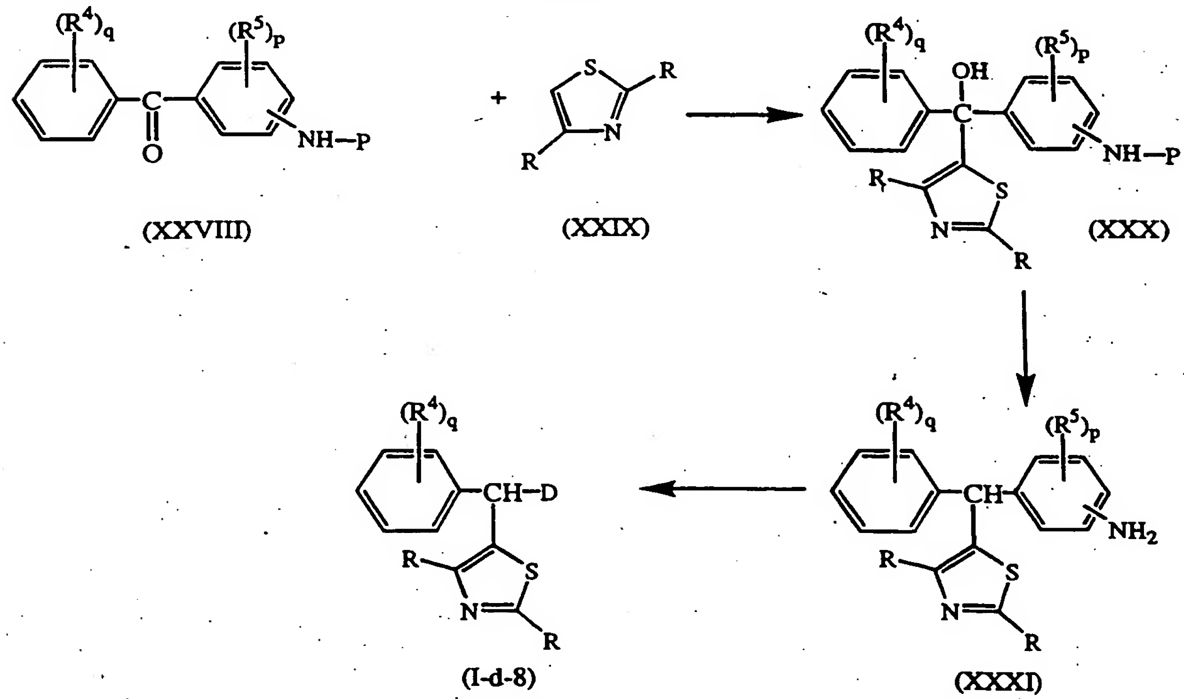
Compounds of formula (I-d) wherein the heterocycle is substituted 2-thiazolyl, said compounds being represented by formula (I-d-7), can be prepared by reacting an

intermediate of formula (XVI) with hydrogensulfide or a functional derivative thereof, in a reaction inert solvent such as, for example, pyridine, optionally in the presence of a suitable base such as, for example, triethylamine, thus forming an intermediate of formula (XXVI), which may subsequently be reacted with an intermediate of formula (XXVII) or a functional derivative thereof such as the ketal derivative thereof, in a reaction-inert solvent such as, for example, ethanol, and optionally in the presence of an acid such as, for example, hydrogenchloride.



Compounds of formula (I-d) wherein the heterocycle is substituted 5-thiazolyl and R^1 is hydrogen, said compounds being represented by formula (I-d-8), can be prepared following the reaction procedure depicted in scheme 4.

Scheme 4

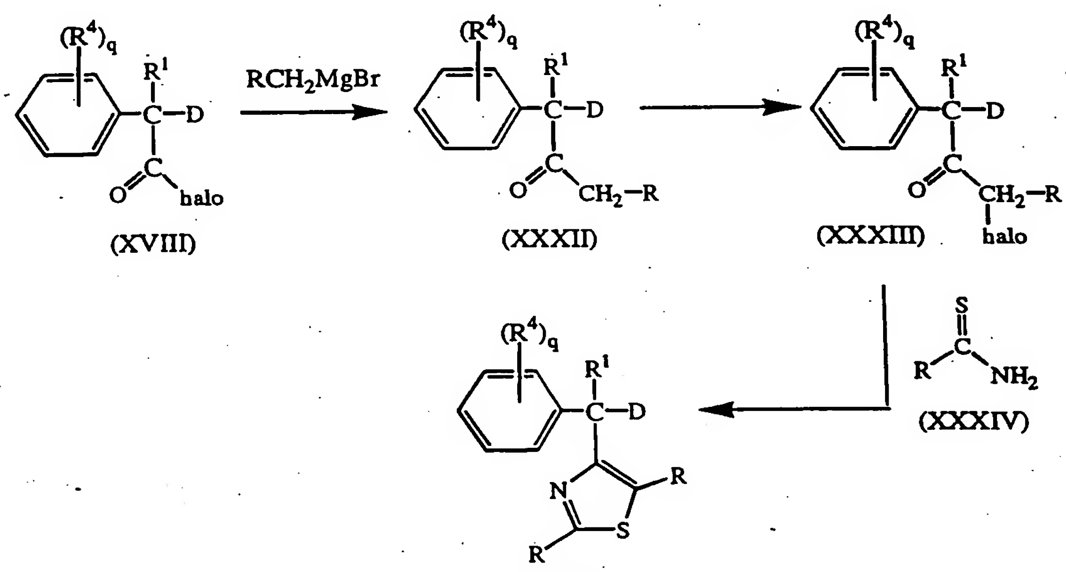


Initially, an intermediate of formula (XXVIII) wherein P is a protective group such as, for example, a C_{1-6}alkylcarbonyl group, is reacted with a thiazole derivative of formula (XXIX) in the presence of a suitable base such as, for example, butyl lithium, in a

reaction inert solvent such as, for example, tetrahydrofuran, thus forming an intermediate of formula (XXX). It may be convenient to perform said reaction under an inert atmosphere at lower temperature, preferably at about -70°C. The hydroxy group and the protective group P of said intermediates (XXX) may be removed using art-known procedures such as, for example, stannous chloride and hydrochloric acid in acetic acid, thus forming an intermediate of formula (XXXI), of which the amino group may further be converted to a 6-azauracil moiety according to the procedure described in EP-A-0,170,316, thus forming a compound of formula (I-d-8).

Also, compounds of formula (I-d) wherein the heterocycle is 4-thiazolyl, said compounds being represented by formula (I-d-9), can be prepared following the reaction procedure depicted in scheme 5.

Scheme 5



An intermediate of formula (XVIII) is reacted with a Grignard reagent of formula RCH_2MgBr or a functional derivative thereofto form an intermediate of formula (XXXII), which may be halogenated, preferably brominated, in the a-position using a suitable reagent such as trimethylphenylammonium tribromide in tetrahydrofuran, thus forming an intermediate of formula (XXXIII). Said intermediate (XXXIII) may then be reacted with a thioamide of formula (XXXIV) to form a compound of formula (I-d-9), in a reaction-inert solvent such as, for example, ethanol, at an elevated temperature, preferably reflux temperature.

The compounds of formula (I) can also be converted into each other following art-

known procedures of functional group transformation of which some examples are mentioned hereinabove.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures.

IL-5, also known as eosinophil differentiating factor (EDF) or eosinophil colony stimulating factor (Eo-CSF), is a major survival and differentiation factor for eosinophils and therefore thought to be a key player in eosinophil infiltration into tissues. There is ample evidence that eosinophil influx is an important pathogenic event in bronchial asthma and allergic diseases such as, cheilitis, irritable bowel disease, eczema, urticaria, vasculitis, vulvitis, winterfeet, atopic dermatitis, pollinosis, allergic rhinitis and allergic conjunctivitis; and other inflammatory diseases, such as eosinophilic syndrome, allergic angiitis, eosinophilic fasciitis, eosinophilic pneumonia, PIE syndrome, idiopathic eosinophilia, eosinophilic myalgia, Crohn's disease, ulcerative colitis and the like diseases.

The present compounds also inhibit the production of other chemokines such as monocyte chemotactic protein-1 and -3 (MCP-1 and MCP-3). MCP-1 is known to attract both T-cells, in which IL-5 production mainly occurs, and monocytes, which are known to act synergetically with eosinophils (Carr et al., 1994, Immunology, *91*, 3652-3656). MCP-3 also plays a primary role in allergic inflammation as it is known to mobilize and activate basophil and eosinophil leukocytes (Baggiolini et al., 1994, Immunology Today, 15(3), 127-133).

The present compounds have no or little effect on the production of other chemokines such as IL-1, IL-2, Il-3, IL-4, IL-6, IL-10, γ-interferon (IFN-γ) and granulocyte-macrophage colony stimulating factor (GM-CSF) indicating that the present IL-5 inhibitors do not act as broad-spectrum immunosuppressives.

The selective chemokine inhibitory effect of the present compounds can be demonstrated by *in vitro* chemokine measurements in human blood of which the test results for IL-5 are presented in the experimental part hereinafter. *In vivo* observations such as the inhibition of eosinophilia in mouse ear, the inhibition of blood eosinophilia in the *Ascaris* mouse model; the reduction of serum IL-5 protein production and splenic IL-5 mRNA expression induced by anti-CD3 antibody in mice and the inhibition of

allergen- or Sephadex-induced pulmonary influx of eosinophils in guinea-pig are indicative for the usefulness of the present compounds in the treatment of eosinophil-dependent inflammatory diseases.

The present inhibitors of IL-5 production are orally active compounds.

In view of the above pharmacological properties, the compounds of formula (I) can be used as a medicine. In particular, the present compounds can be used in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases as mentioned hereinabove, more in particular bronchial asthma, atopic dertmatitis, allergic rhinitis and allergic conjunctivitis.

In view of the utility of the compounds of formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from eosinophil-dependent inflammatory diseases, in particular bronchial asthma, atopic dertmatitis, allergic rhinitis and allergic conjunctivitis. Said method comprises the systemic or topical administration of an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

The present invention also provides compositions for treating eosinophil-dependent inflammatory diseases comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as oral, percutaneous, or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier

will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gellies, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. Application of said compositions may be by aerosol, e.g. with a propellent such as nitrogen, carbon dioxide, a freon, or without a propellent such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

Appropriate cyclodextrins are α-, β-, γ-cyclodextrins or ethers and mixed ethers thereof

wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyC_{1-6}alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyC_{1-6}alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6}alkylcarbonyl, particularly acetyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or carboxy-C_{1-6}alkyloxyC_{1-6}alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD (2-HP-β-CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S.value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10.

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the D.S. ranges from 0.125 to 3.

Due to their high degree of selectivity as IL-5 inhibitors, the compounds of formula (I) as defined above, are also useful to mark or identify receptors. To this purpose, the compounds of the present invention need to be labelled, in particular by replacing, partially or completely, one or more atoms in the molecule by their radioactive isotopes. Examples of interesting labelled compounds are those compounds having at least one halo which is a radioactive isotope of iodine, bromine or fluorine; or those compounds having at least one ^{11}C-atom or tritium atom.

One particular group consists of those compounds of formula (I) wherein R^3 and/or R^4 are a radioactive halogen atom. In principle, any compound of formula (I) containing a halogen atom is prone for radiolabelling by replacing the halogen atom by a suitable isotope. Suitable halogen radioisotopes to this purpose are radioactive iodides, e.g.

^{122}I, ^{123}I, ^{125}I, ^{131}I; radioactive bromides, e.g. ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br, and radioactive fluorides, e.g. ^{18}F. The introduction of a radioactive halogen atom can be performed by a suitable exchange reaction or by using any one of the procedures as described hereinabove to prepare halogen derivatives of formula (I).

Another interesting form of radiolabelling is by substituting a carbon atom by a ^{11}C-atom or the substitution of a hydrogen atom by a tritium atom.

Hence, said radiolabelled compounds of formula (I) can be used in a process of specifically marking receptor sites in biological material. Said process comprises the steps of (a) radiolabelling a compound of formula (I), (b) administering this radio-labelled compound to biological material and subsequently (c) detecting the emissions from the radiolabelled compound. The term biological material is meant to comprise every kind of material which has a biological origin. More in particular this term refers to tissue samples, plasma or body fluids but also to animals, specially warm-blooded animals, or parts of animals such as organs.
The radiolabelled compounds of formula (I) are also useful as agents for screening whether a test compound has the ability to occupy or bind to a particular receptor site. The degree to which a test compound will displace a compound of formula (I) from such a particular receptor site will show the test compound ability as either an agonist, an antagonist or a mixed agonist/antagonist of said receptor.
When used in *in vivo* assays, the radiolabelled compounds are administered in an appropriate composition to an animal and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of the particular receptor sites throughout the body can be detected and organs containing said receptor sites can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of formula (I) and detecting the emissions from the radioactive compound also constitutes a part of the present invention.

In general, it is contemplated that a therapeutically effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.05 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

Experimental part

Hereinafter, the term 'RT' means room temperature, 'THF' means tetrahydrofuran,

'EtOAc' means ethylacetate, 'DMF' means *N,N*-dimethylformamide, 'MIK' means methylisobutyl ketone, 'DIPE' means diisopropylether, and 'HOAc' means acetic acid.

A. Preparation of the intermediate compounds

Example A.1

a) A solution of 4-chloro-3-(trifluoromethyl)benzeneacetonitrile (0.114 mol) in THF (100ml) was added dropwise at RT to a solution of 1,2,3-trichloro-5-nitrobenzene (0.114 mol) and *N,N,N*-triethylbenzenemethanaminium chloride (3g) in NaOH (150ml) and THF (100ml). The mixture was stirred for 2 hours, then poured out on ice, acidified with a concentrated HCl solution and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 40.4 g (86.5%) of (±)-2,6-dichloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-4-nitrobenzene-acetonitrile (interm. 1).

b) A solution of intermediate (1) (0.0466 mol), iodomethane (0.0606 mol), KOH (0.1864 mol) and *N,N,N*-triethylbenzenemethanaminium chloride (0.0466 mol) in toluene (200ml) was stirred at 50°C for 2 hours. The mixture was poured out into water, acidified with HCl 3N and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 90/10). The pure fractions were collected and the solvent was evaporated, yielding 11g (55%) of (±)-2,6-dichloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-α-methyl-4-nitrobenzene-acetonitrile (interm. 2).

c) A mixture of intermediate (2) (0.0259 mol) in methanol (200ml) was hydrogenated at 40°C overnight with platinum-on-charcoal catalyst 1% (1g) as a catalyst in the presence of thiophene 10% in ethanol (1 ml). After uptake of hydrogen (3 equivalents), the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated, yielding 10g (98%) of (±)-4-amino-2,6-dichloro-α-[4-chloro-3-(trifluoro-methyl)phenyl]-α-methylbenzeneacetonitrile (interm. 3).

Example A.2

a) A solution of $NaNO_2$ (0.0243 mol) in water (10ml) was added dropwise at 5°C to a solution of intermediate (3) (0.0243 mol) in HOAc (75ml) and concentrated HCl (20ml). The mixture was stirred at 0°C for 35 minutes and then added dropwise to a solution of ethyl cyanoacetylcarbamoate (0.0326 mol) and sodium acetate (112g) in water (1300ml), cooled to 0°C. The mixture was stirred at 0°C for 45 minutes. The precipitate was filtered off, washed with water and taken up in CH_2Cl_2. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated,

yielding 15.2g of (±)-ethyl 2-cyano-2-[[3,5-dichloro-4-[1-[4-chloro-3-(trifluoromethyl)-phenyl]-1-cyanoethyl]phenyl]hydrozono]-1-oxoethylcarbamate (interm. 4).

b) A mixture of intermediate (4) (0.0271 mol) and potassiumacetate (0.0285 mol) in HOAc (150ml) was stirred and refluxed for 3 hours and then poured out on ice. The precipitate was filtered off, washed with water and taken up in EtOAc. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated, yielding 12g (86%) of (±)-2-[3,5-dichloro-4-[1-[4-chloro-3-(trifluoromethyl)phenyl]-1-cyanoethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (interm. 5).

c) A mixture of intermediate (5) (0.0223 mol) in HCl (40ml) and HOAc (150ml) was stirred and refluxed for 3 hours and then poured out into ice water. The precipitate was filtered off, taken up in CH_2Cl_2 and CH_3OH, washed with water, dried, filtered and the solvent was evaporated, yielding 11.4g (96%) of (±)-2-[3,5-dichloro-4-[1-[4-chloro-3-(trifluoromethyl)phenyl]-1-cyanoethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 6).

d) A mixture of intermediate (6) (0.05 mol) in 2-mercaptoacetic acid (60 ml) was stirred and refluxed for 140 minutes. The reaction mixture was allowed to cool to RT, then poured out into ice-water. The mixture was stirred, then decanted. CH_2Cl_2/CH_3OH (300 ml, 90/10) was added to the residue. The organic layer was separated, washed with an aqueous $NaHCO_3$ solution (200 ml) and with water, then dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 99/1). The desired fractions were collected and the solvent was evaporated, yielding 28 g of (±)-2,6-dichloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-methylbenzeneacetonitrile (interm. 7).
(±)-2-chloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-5,α-dimethylbenzeneacetonitrile was prepared following the same procedure as described in example A2d (interm. 8).

e) A mixture of intermediate (7) (0.0106 mol) and triethylamine (0.0106 mol) in pyridine (70 ml) was stirred at 60°C. Gaseous H_2S was bubbled through the mixture for 8 hours. The mixture was stirred at 60°C overnight. Gaseous H_2S was bubbled through the mixture for another 10 hours. The mixture was stirred at 60°C overnight. The solvent was evaporated. The residue was taken up in EtOAc, washed with a diluted HCl solution and with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated, yielding 2.5g (45%) of (±)-2,6-dichloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-methylbenzeneethanethioamide (interm. 9).

Following the same procedure there were also prepared :
(±)-2-chloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-4-[4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl]-5,α-dimethylbenzeneethanethioamide (interm. 10);
(±)-2,6-dichloro-α-(3,4-dichlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-methylbenzeneethanethioamide (interm. 11);
(±)-2-chloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-4-[4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl]-α-methylbenzeneethanethioamide (interm. 12);
(±)-2-chloro-α-(4-chlorophenyl)-α-methyl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneethanethioamide (interm. 13);
(±)-2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-methylbenzeneethanethioamide (interm. 14);
(±)-2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneethanethioamide (interm. 15).

Example A.3

a) A mixture of intermediate (1) (0.138 mol) in methanol (300ml) was hydrogenated at RT under a 3 bar pressure for 1 hour with Raney Nickel (50g) as a catalyst in the presence of thiophene solution 10% in ethanol (5ml). After uptake of hydrogen (3 equivalents), the catalyst was filtered through celite, washed with methanol and CH_2Cl_2 and the filtrate was evaporated, yielding 49.5g (94%) of (±)-4-amino-2,6-dichloro-α-[4-chloro-3-(trifluoromethyl)phenyl]benzeneacetonitrile (interm. 16).

b) (±)-2,6-dichloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneethanethioamide was prepared following the same procedure as decribed in A1c and A2a through A2e (interm. 17).

c) Acetic anhydride (0.1268 mol) was added dropwise at RT to a solution of intermediate (16) (0.0634 mol) in toluene (200ml). The mixture was stirred and refluxed for 3 hours, then cooled, poured out into H_2O and extracted with EtOAc. The organic layer was separated, washed with K_2CO_3 10% and with H_2O, dried, filtered and the solvent was evaporated, yielding 27.9g (±)-*N*-[3,5-dichloro-4-[[4-chloro-3-(trifluoromethyl)-phenyl]cyanomethyl]phenyl]acetamide (interm. 18; mp. 172°C).

Example A.4

a) n-Butyllithium 1.6 M (0.135 mol) was added dropwise at -70°C under N_2 flow to a solution of 3-bromopyridine (0.11 mol) in 1,1'-oxybisethane (250ml). The mixture was stirred at -70°C for 1 hour. A solution of 2,4'-dichloro-4-nitrodiphenylmethanone (0.0844 mol) in THF (200ml) was added dropwise. The mixture was stirred at -70°C for 3 hours, then poured out into water and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified

by column chromatography over silica gel (eluent: cyclohexane/EtOAc 60/40 to 100/0). The pure fractions were collected and the solvent was evaporated, yielding 13.7g (43%) of (±)-α-(2-chloro-4-nitrophenyl)-α-(4-chlorophenyl)-3-pyridinemethanol (interm. 19).

b) A mixture of intermediate (19) (0.0373 mol) in methanol (150ml) was hydrogenated at RT under a 3 bar pressure for 4 hours with Raney Nickel (14g) as a catalyst in the presence of thiophene solution 1% in ethanol (2.5ml). After uptake of hydrogen (3 equivalents), the catalyst was filtered through celite and the filtrate was evaporated, yielding 12.06g (94%) of (±)-α-(4-amino-2-chlorophenyl)-α-(4-chlorophenyl)-3-pyridinemethanol (interm. 20).

c) Formamide (60ml) was added to a mixture of intermediate (20) (0.0349 mol) in HOAc (60ml). The mixture was stirred at 150°C for 6 hours, cooled, poured out into ice water, basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 14.1g of (±)-*N*-[3-chloro-[4-[(4-chlorophenyl)-3-pyridinylmethyl]phenyl]formamide (interm. 21).

d) A mixture of intermediate (21) (0.0349 mol) in HCl 6N (150ml) was stirred and refluxed for 4 hours, then cooled, poured out on ice, basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98.5/1.5/0.1). The pure fractions were collected and the solvent was evaporated, yielding 7.2g (63%) of (±)-3-chloro-4-[(4-chlorophenyl)-3-pyridinylmethyl]benzenamine (interm. 22).

e) (±)-2-[3-chloro-4-[(4-chlorophenyl)-3-pyridinylmethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid was prepared following the same procedure as decribed in A1c and A2a through A2c (interm. 23).

<u>Example A.5</u>

a) A mixture of (±)-α-(2-chloro-4-nitrophenyl)-α-(4-chlorophenyl)-1-methyl-1*H*-imidazole-2-methanol (0.0397 mol) and $SnCl_2$ (0.2382 mol) in HOAc (150ml) and HCl (150ml) was stirred and refluxed for 2 hours, then cooled, poured out on ice, basified with NH_4OH, filtered over celite and extracted with CH_2Cl_2 and CH_3OH. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 12g (91%) of (±)-3-chloro-4-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-2-yl)methyl]benzenamine (interm. 24).

b) (±)-2-[3-chloro-4-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-2-yl)methyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 25); (±)-2-[3-chloro-4-[(4-chlorophenyl)(1-methyl-1*H*-1,2,4-triazol-5-yl)methyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 26); and

(±)-2-[3-chloro-4-[(4-chlorophenyl)(2-methyl-4-phenyl-5-thiazolyl)methyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 27) were prepared following the same procedure as decribed in A1c and A2a through A2c.

<u>Example A.6</u>

a) α-(4-chlorophenyl)-4-pyridinemethanol (0.0512 mol), *N*-(3,5-dichlorophenyl)-acetamide (0.102 mol) and polyphosphoric acid (210g) were stirred at 140°C for 90 minutes. The mixture was cooled to 100°C, poured out into ice water, basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was taken up in 2-propanone and diethyl ether. The precipitate was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 97.5/2.5/0.1). The pure fraction was collected and the solvent was evaporated, yielding 17.94g (87%) of (±)-*N*-[3,5-dichloro-4-[(4-chlorophenyl)-4-pyridinylmethyl]phenyl]-acetamide (interm. 28).

b) The following products were prepared as described in A4c through A4e :
(±)-2-[3,5-dichloro-4-[(4-chlorophenyl)-4-pyridinylmethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 29);
(±)-2-[3,5-dichloro-4-[(4-chlorophenyl)-2-pyridinylmethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 30);
(±)-2-[3-chloro-4-[(2-chlorophenyl)-2-pyridinylmethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 31);
(±)-2-[3,5-dichloro-4-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-2-yl)methyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 32); and
(±)-2-[3,5-dichloro-4-[(4-chlorophenyl)-3-pyridinylmethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 33).

<u>Example A.7</u>

a) A mixture of 4-isothiocyanato-2-(trifluoromethyl)-α-[3-(trifluoromethyl)phenyl]-benzeneacetonitrile (0.0516 mol), NaOH solution, 50% (0.155 mol) and *N,N,N*-triethyl-benzenemethanaminium chloride (0.0052 mol) in toluene (250 ml) was stirred for 4 hours under O_2 at RT. Ice-water and HOAc (9.3 ml) were added. Toluene was added and the reaction mixture was stirred vigorously. The layers were separated. The separated organic layer was dried, filtered and the solvent evaporated. The residue was stirred in hexane. The precipitate was filtered off, washed, and dried, yielding 15.8 g (97.2%) of (4-amino-2-chlorophenyl)[4-chloro-3-(trifluoromethyl)phenyl]methanone (interm. 34).

b) (±)-2-[3-chloro-4-[4-chloro-3-(trifluoromethyl)benzoyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 35) was prepared following the procedures described in A1c and A2a through A2d.

c) A mixture of intermediate (35) (0.013 mol) in methanol (50 ml) and THF (50 ml) was stirred at RT. $NaBH_4$ (0.013 mol) was added portionwise. The reaction mixture was stirred for 1 hour, then acidified (to pH = ± 6) with concentrated hydrochloric acid. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The desired fractions were collected and the solvent was evaporated, yielding 5.3 g (94.2%) of (±)-2-[3-chloro-4-[[4-chloro-3-(trifluoromethyl)-phenyl]hydroxymethyl]phenyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 36).
In a similar way, there was also prepared 2-[3,5-dichloro-4-[(4-fluorophenyl)-hydroxymethyl]phenyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 37).

d) Thionylchloride (5 ml) was added dropwise to a mixture of intermediate (30) (0.012 mol) in CH_2Cl_2 (50 ml), stirred at RT. The resulting reaction mixture was stirred and refluxed for 2 hours. The solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 4.9 g (90.4%) of (±)-2-[3-chloro-4-[chloro[4-chloro-3-(trifluoromethyl)phenyl]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 38).
Following the same procedure, there were also prepared :
2-[3,5-dichloro-4-[chloro[4-chloro-3-(trifluoromethyl)phenyl]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 39);
(±)-2-[3-chloro-4-[chloro(4-chlorophenyl)-2-thiazolylmethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 40); and
(±)-2-[4-[(2-benzothiazolyl)chloro(4-chlorophenyl)methyl-3-chlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 41).

Example A.8

a) K_2CO_3 (0.1786 mol) was added to a solution of intermediate (18) (0.0638 mol) in dimethylsulfoxide (100ml) and water (10ml). Air was bubbled through the mixture for 72 hours. The mixture was poured out into H_2O. The precipitate was filtered off and taken up in EtOAc. The organic solution was washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.25/0.75). The pure fractions were collected and the solvent was evaporated, yielding 18.6g (72%) of *N*-[3,5-dichloro-4-[4-chloro-3-(trifluoromethyl)benzoyl]phenyl]acetamide (interm. 42).

b) 2-[3,5-dichloro-4-[4-chloro-3-(trifluoromethyl)benzoyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 43) was prepared following the procedure as described in A6b.

c) 2-[3,5-dichloro-4-[4-chloro-3-(trifluoromethyl)benzoyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 44) was prepared following the procedure as described in A2d.
d) 2-[3,5-dichloro-4-[[4-chloro-3-(trifluoromethyl)phenyl]hydroxymethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 45) was prepared following the procedure as described in A7c.

Example A 9

a) A mixture of 4-chloro-α-[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-phenyl]-α-methyl-3-(trifluoromethyl)benzeneacetonitrile (0.009 mol) in H_2SO_4 (50ml), HOAc (50ml) and H_2O (40ml) was stirred and refluxed overnight. The mixture was poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated, yielding 4.2g of (±)-2-chloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-4-[4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl]-α-methylbenzeneacetic acid (interm. 46).
b) A mixture of intermediate (46) (0.009 mol) in thionyl chloride (25ml) was stirred and refluxed for 2.5 hours. The solvent was evaporated, yielding (±)-2-chloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-4-[4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl]-α-methyl-benzeneacetyl chloride (interm. 47).
Following the same procedure, there were also prepared :
(±)-2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-benzeneacetyl chloride (interm. 48); and
(±)-2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-α-methylbenzeneacetyl chloride (interm. 49).
c) A solution of intermediate (48) (0.011 mol) in 2-propanone (25ml) was added at RT to a solution of *N*-hydroxy benzenecarboximidamide (0.011 mol) and K_2CO_3 (0.011 mol) in 2-propanone (25ml). The mixture was stirred at RT overnight. The precipitate was filtered off, washed with water and taken up in CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 1.4g (25%) of (±)-(iminophenylmethyl)amino 2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-(4-chlorophenyl)benzeneacetate (interm. 50).
Following the same procedure, there was also prepared :
(±)-(iminophenylmethyl)amino 2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-methylbenzeneacetate (ester) (interm. 51).
d) A solution of intermediate (48) (0.0365 mol) in CH_2Cl_2 (70ml) was added at RT to a solution of 2-aminophenol (0.073 mol) in CH_2Cl_2 (280ml). The mixture was stirred at RT for 12 hours, then washed with HCl 3N and with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was

evaporated, yielding 3.8g (21%) of (±)-α-(4-chlorophenyl)-3-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-*N*-(2-hydroxyphenyl)benzeneacetamide (interm. 52).

In a similar manner there were also prepared :

(±)-2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetic acid 2-benzoylhydrazide (interm. 53);

(±)-(benzoylamino)-2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazine-2(3*H*)-yl)benzeneacetamide (interm. 54);

(±)-2-chloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-methylbenzeneacetic acid 2-benzoylhydrazide (interm. 55);

(±)-2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-*N*-(2-hydroxyphenyl)-α-methylbenzeneacetonitrile (interm. 56);

(±)-2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-benzeneacetic acid 2-acetylhydrazide (interm. 57);

(±)-2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-*N*-(2-phenyl-2-oxoethyl)benzeneacetamide (interm. 58);

(±)-2-[[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-3(2*H*)-yl)phenyl] (4-chloro-phenyl)acetyl]-*N*-phenylhydrazinecarbothioamide (interm. 59);

(±)-2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-methylbenzeneacetic acid 2-benzoylhydrazide (interm. 60); and

(±)-2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4,-triazin-2(3*H*)-yl)-*N*-(2-phenyl-2-oxoethyl)benzeneacetamide (interm. 61).

Example A 10

a) A mixture of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5-(2*H*,4*H*)-dione (0.03 mol), thiourea (0.03 mol) and $NaHCO_3$ (0.03 mol) in DMF (75 ml) was stirred for 18 hours at RT. The solvent was evaporated. The residue was stirred in water, filtered off, washed with water, yielding 12.3 g. (±)-[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]-4-(chloro-phenyl)methyl carbamimidothioate (interm. 62).

b) A mixture of NaOH (0.25 mol) in water (100 ml) was stirred at RT. (0.03 mol) was added and the resulting reaction mixture was stirred for 18 hours at RT, neutralized, and the precipitate was filtered off and dissolved in CH_2Cl_2. The aqueous phase was separated. The separated organic layer was dried, filtered, and the solvent evaporated. The residue was purified over silica gel on a glass filter (eluent: $CH_2Cl_2/CH_3OH/THF$ 92/3/5). The desired fractions were collected and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/THF$ 92/3/5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried, yielding 4.2 g

(37%) (±)-2-[3-chloro-4-[(4-chlorophenyl)mercaptomethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 63).

Example A.11

a) A mixture of 2-[3-chloro-4-(4-chlorobenzoyl)phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.081 mol) in formic acid (120 ml) and formamide (300 ml) was stirred for 16 hours at 160 °C. The reaction mixture was cooled, poured out into water (600 ml) and the resulting precipitate was filtered off and dried. This fraction was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, and dried, yielding 8.78 g (22.5%) of (±)-*N*-[[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl](4-chlorophenyl)methyl]formamide (interm. 64).

b) A mixture of intermediate (64) (0.277 mol) in HCl (200 ml, 36%) and HOAc (1000 ml) was stirred and refluxed for 1 hour. The solvent was evaporated. The residue was taken up into water, then basified with K_2CO_3. The precipitate was filtered off, dried and stirred in boiling ethanol, cooled, filtered off and dried. The precipitate was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling CH_3CN, then cooled, filtered off and dried, yielding 1.1 g (±)-2-[4-[amino(4-chlorophenyl)methyl]-3-chlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 65).

Example A 12

$NaOCH_3$ (0.189 mol; 30 % in CH_3OH) was added to a solution of hydroxylamine (0.189 mol) in ethanol (105ml) The mixture was stirred at RT for 15 minutes and then filtered. The fitrate was added to a mixture of 2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2-(3*H*)-yl)benzeneacetonitrile (0.054 mol) in ethanol (55ml). The mixture was stirred at 60°C for 1 hour, stirred and refluxed for 2 hours and stirred at RT overnight. The solvent was evaporated. The residue was taken up in water and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 20.3g of (±)-2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-*N*'-hydroxybenzeneethanimidamide (interm. 66).

Example A13

a) Trifluoro acetic acid (100ml), previously cooled to 5°C, was added dropwise at 0°C/5°C under N_2 flow to (±)-1,1-dimethylethyl-2-[2-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]-2-(4-chlorophenyl)acetyl]hydrazinecarboxylate (0.035 mol). The mixture was allowed to warm to RT and then stirred for 1 hour. The solvent was evaporated. The residue was taken up in H_2O. The precipitate was filtered

off, dried, washed with DIPE and dried, yielding 11g (70%) of R142321 (interm. 67).

b) A mixture of 3-hydroxy-benzoyl chloride (0.0124 mol) in THF (25ml) was added dropwise at 10°C under N_2 flow to a solution of intermediate 67 (0.0113 mol) and triethylamine (0.0452 mol) in THF (30ml). The mixture was brought to RT. HCl 3N was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was taken up in ethanol. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated, yielding 3g (47%) of (±)-2-[3,5-dichloro-4-[1-(4-chlorophenyl)-2-[(3-hydroxybenzoyl)hydrazino]-2-oxoethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 68)

Example A14

a) A mixture of 2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4,-triazin-2(3*H*)-yl)-benzeneacetyl chloride (0.05 mol) in THF (200 ml) was stirred at -75°C. A solution of chloroethyl magnesium (0.1 mol; 2 M/THF) in THF (50 ml) was added dropwise at -75°C. The reaction mixture was stirred for 90 minutes, then the temperature was raised to -20 °C. A saturated aqueous NH_4Cl solution was added dropwise. Water was added and the product was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was filtered over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). Two fractions were collected and the solvent was evaporated, yielding 3.8 g (±)-2-[3,5-dichloro-4-[1-(4-chlorophenyl)-2-oxobutyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 69).

b) A mixture of intermediate 69 (0.005 mol) in 1,4-dioxane (10 ml) and diethyl ether (20 ml) was stirred at RT. Br_2 (0.005 mol) was added dropwise at RT and the resulting reaction mixture was stirred for 15 hours at RT. This mixture was washed 3 times with water and CH_2Cl_2 was added. The separated organic layer was dried, filtered and the solvent evaporated. The residue was dried, yielding 2.6 g (±)-2-[4-[3-bromo-1-(4-chlorophenyl)-2-oxobutyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 70).

Example A15

a) *n*-Butyl lithium (0.045 mol) was added at -70°C under N_2 flow to a solution of 4-phenyl-thiazole (0.045 mol) in diethyl ether (50ml). The mixture was stirred at -70°C for 90 minutes. A solution of 2-[3-chloro-4-(4-chlorobenzoyl)phenyl]-1,2,4-triazine-3,5-(2*H*,4*H*)-dione (0.015 mol) in THF (10ml) was added at -70°C. The mixture was stirred at -70°C for 1 hour, then poured out into ice water, neutralized with HCl 3N and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent

wasevaporated. The residue was purified by column chromatography oversilica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The desired fraction was repurified by HPLC (eluent: $CH_3OH/(NH_4OAc$ 1% in $H_2O)$ 80/20). The pure fractions were collected and the solvent was evaporated, yielding 0.83g (11%) of (±)-2-[3-chloro-4-[(4-chlorophenyl)-hydroxy(4-phenyl-2-thiazolyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 71).

b) A mixture of intermediate 71 (0.0076 mol) in thionyl chloride (35ml) was stirred at 50°C for 4 hours and then brought to RT. The solvent was evaporated, yielding (±)-2-[3-chloro-4-[chloro(4-chlorophenyl)(5-chloro-4-phenyl-2-thiazolyl)methyl]-phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (interm. 72).

Example A16

a) 1-Chloromethoxy-2-methoxy-ethane (0.147 mol) was added dropwise at 15°C to a solution of 3-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (0.134 mol) and K_2CO_3 (0.134 mol) in DMF (200ml). The mixture was stirred at RT for 24 hours, then poured out into H_2O and extracted with diethyl ether. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated, yielding 67.27g (±)-2-chloro-α-(4-chlorophenyl)-4-[4,5-dihydro-4-[(2-methoxyethoxy)methyl]-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl]benzeneacetonitrile (interm. 73).

b) NaH (0.063 mol) was added at 10°C under N_2 flow to a solution of intermediate 73 (0.0485 mol) in DMF (100ml). The mixture was stirred for 30 minutes. A solution of 2-chloromethyl-4-phenyl-thiazole (0.063 mol) in DMF (100ml) was added. The mixture was allowed to warm to 15°C over a 2-hour period while stirring, then poured out into ice water and extracted with diethyl ether. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 65/35). The pure fractions were collected and the solvent was evaporated, yielding 15g (52%) of (±)-α-[2-chloro-4-[4,5-dihydro-4-[(2-methoxyethoxy)methyl]-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl]phenyl]-α-(4-chlorophenyl)-4-phenyl-2-thiazolpropanenitrile (interm. 74)

c) A mixture of intermediate 74 (0.0186 mol) in H_2SO_4 (160ml), acetic acid (160ml) and H_2O (25ml) was stirred and heated for 48 hours. The mixture was cooled and poured out into H_2O. The precipitate was filtered off, taken up in EtOAc and the mixture was separated into its layers. The organic layer was dried, filtered and the solvent was evaporated, to give residue 1. The aqueous layer was evaporated partially and then cooled. The precipitate was filtered off and taken up in EtOAc. The organic solution was dried, filtered and the solvent was evaporated, to give residue 2. Residue 1 and 2 were combined, yielding 8.97g (86%) of (±)-α-[2-chloro-4-[4,5-dihydro-3,5-dioxo-

1,2,4-triazin-2(3*H*)-yl]phenyl]-α-(4-chlorophenyl)-4-phenyl-2-thiazolpropanoic acid (interm. 75).

Example A17

a) NaH (0.0772 mol) was added portionwise at 0°C under N_2 flow to a mixture of 4-chloro-benzeneacetonitrile (0.0643 mol) in DMF (50ml). The mixture was stirred at 0°C under N_2 flow for 1 hour. A mixture of 1,3-dibromo-2-methoxy-5-nitro-benzene (0.0643 mol) in DMF (50ml) was added at 0°C under N_2 flow. The mixture was stirred at RT for 3 hours, hydrolized with H_2O and HCl 3N and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/cyclohexane 60/40). The pure fractions were collected and the solvent was evaporated, yielding 12.8g (46%) of (±)-2,6-dibromo-α-(4-chlorophenyl)-4-nitrobenzeneacetonitrile (interm. 76).

b) $TiCl_3$ (0.13 mol; 15 % in H_2O) was added dropwise at RT to a solution of intermediate 76 (0.026 mol) in THF (200ml). The mixture was stirred at RT for 2 hours, poured out into H_2O and extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O and with K_2CO_3 10%, dried, filtered and the solvent was evaporated. 2 g of this fraction was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 1.3g (±)-4-amino-2,6-dibromo-α-(4-chlorophenyl)-benzene-acetonitrile (interm. 77).

B. Preparation of the final compounds

Example B1

A mixture of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.0075 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.025 mol) in 2-methylpropanol (25 ml) was stirred for 72 hours at 80 °C. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97.5/2.5). The pure fractions were collected and the solvent was evaporated. The residue was dried, yielding 0.8 g (25%) of (±)-2-[3-chloro-4-[(4-chloro-phenyl)(2-methylpropoxy)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4 *H*)-dione (compound 133).

Example B2

a) A mixture of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.015 mol) and 2-mercaptopyridine (0.04 mol) in THF (100 ml) was stirred overnight at RT. 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mol) was added and the resulting reaction mixture was stirred for 3 hours. NaOH (1 N; 50 ml) was added. The mixture was stirred for 5 minutes, then extracted with EtOAc. The separated organic layer was washed with water, dried, filtered and the solvent evaporated. The

aqueous layers were combined, then acidified (pH = 6) with HCl (1 N). This mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/THF/CH_3OH 94/5/1). The pure fractions were collected and the solvent was evaporated. The residue was stirred overnight in diethyl ether. The solvent was evaporated. The residue was dried, yielding 2.98 g (43%) (±)-2-[3-chloro-4-[(4-chlorophenyl)(2-pyridinyl-thio)methyl] phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 93).

b) (±)-2-[3-chloro-4-[(4-chlorophenyl)(1*H*-imidazol-2-ylthio)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione was prepared using the same procedure as in example B2a, but using $NaHCO_3$ as a base and DMF as a solvent (compound 94).

c) Sodium (0.075 mol) was added portionwise to ethanol (50 ml) under N_2 atmosphere and this mixture was stirred until complete dissolution. Ethyl 2-amino-3-mercaptopropanoate (0.075 mol) was added and the mixture was stirred for 2 hours at RT. The solvent was evaporated, THF (50 ml) was added to the residue, and a solution of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.015 mol) in THF (50 ml) was added. 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mol) was added and the resulting reaction mixture was stirred overnight at RT. The solvent was evaporated. The residue was stirred in water and extracted with CH_2Cl_2. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated. This fraction was purified by HPLC over silica gel (eluent: CH_2Cl_2/CH_2OH 97/3). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried, yielding (±)-ethyl α-[[[(4-chlorophenyl)[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]methyl]thio]methyl]glycine (compound 95).

d) A mixture of intermediate 39 (0.00618 mol), 5-amino-4-phenyl-2(3*H*)-thiazole-thione (0.00742 mol) and 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (0.0124 mol) in dry THF (50 ml) and DMF (50 ml) was stirred and refluxed for four days under N_2 atmosphere. The solvent was evaporated. The residue was taken up into CH_2Cl_2/CH_3OH (95/5). The organic solution was washed twice with a saturated aqueous NaCl solution, dried, filtered and the solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97.5/2.5). The desired fractions were collected and the solvent was evaporated. The residue was repurified by HPLC over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0 first 30 minutes, then 95/5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling CH_3CN, then allowed to cool to RT. The precipitate was filtered off, washed with CH_3CN, then dried, yielding 0.24 g of (±)-2-[3,5-dichloro-4-

[[4-chloro-3-(trifluoromethyl)phenyl][(2,3-dihydro-5-phenyl-2-thioxo-1*H*-imidazol-4-yl)thio]-methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 400).

Example B3

a) A mixture of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.015 mol) and 1-methylpiperazine (0.04 mol) in DMF (100 ml) was stirred for 24 hours at 80 °C. The solvent was evaporated. MIK was added and azeotroped on the rotary evaporator. The residue was stirred in water, then extracted with CH_2Cl_2. The separated organic layer was washed with water, dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/THF 90/5/5 and CH_2Cl_2/CH_3OH 90/10). The pure fractions were collected and the solvent was evaporated. The residue was stirred overnight in DIPE, then the solvent was evaporated. The residue was crystallized from EtOAc. The precipitate was filtered off, washed with EtOAc, DIPE, then dried, yielding 1.19 g (±)-2-[3-chloro-4-[(4-chlorophenyl)(4-methyl-1-piperazinyl) methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 118).

b) A mixture of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.015 mol), 4-hydroxypiperidine (0.02 mol) and sodiumbicarbonate (0.02 mol) in DMF (100ml) was stirred for 16 hours at 80 °C. The mixture was cooled. The solvent was evaporated. The residue was purified by columnchromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried, yielding 0.070 g (±)-2-[3-chloro-4-[(4-chlorophenyl)(4-hydroxy-1-piperidinyl) methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 119).

c) (±)-2-[3-chloro-4-[(4-chlorophenyl)[(2-hydroxyethyl)amino]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione was prepared according to the procedure described in example B3a but using CH_3CN as a solvent instead of DMF (compound 51).

d) Methanol (100 ml) was stirred at RT and sodium (0.09 mol) was added. The mixture was stirred until complete dissolution. (1*H*-imidazol-2-yl)methanamine (0.045 mol) was added. The mixture was stirred for 30 minutes. NaCl was removed by filtration and the filtrate was evaporated. Toluene was added and azeotroped on the rotary evaporator. 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.015 mol) and acetonitrile (50 ml) were added. The resulting reaction mixture was stirred and refluxed for 20 hours. The solvent was evaporated, the residue was stirred in water, and extracted with CH_2Cl_2/CH_3OH (90/10). The separated organic layer was dried, filtered, and the solvent evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 90/10). The pure fractions were collected and the solvent was evaporated. The residue was stirred in CH_3CN, filtered

off, washed with DIPE, then dried, yielding 1.1 g (16.5%) of (±)-2-[3-chloro-4-[(4-chlorophenyl)[(1*H*-imidazol-2-ylmethyl)amino]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 50).

e) (±)-2-[3-chloro-4-[(4-chlorophenyl)(2-pyrimidinylamino)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione was prepared according to the procedure described in example B3a but using acetic acid as a solvent instead of DMF (compound 49).

f) (±)-2-[3-chloro-4-[(4-chlorophenyl)[(1-methyl)-4-piperidinyl)amino]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4 *H*)-dione was prepared according to the procedure described in example B3a but using THF as a solvent instead of DMF (compound 48).

g) A mixture of 2-[4-[chloro(4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.00719 mol) and 2-pyrimidinamine (0.00863 mol) was heated for 2 hours at 150 °C in an autoclave. The mixture was cooled to RT. This fraction was taken up into CH_2Cl_2, washed with water, dried, filtered and the solvent was evaporated. The residue was purified by HPLC (eluent: (0.5% NH_4OAc in H_2O)/CH_3OH/CH_3CN gradient elution from 70/15/15 over 0/50/50 to 0/0/100). The desired fractions were collected and the solvent was evaporated. The residue was coevaporated with EtOAc. The residue was stirred in DIPE, filtered off, washed and dried, yielding 0.21 g of (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)[(2-pyrimidinyl)amino]-methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 413).

Example B4

a) n-Butyllithium, 1.6M (0.0414 mol) was added dropwise at -70°C under N_2 flow to a solution of 1-methyl-1*H*-imidazole (0.0414 mol) in diethyl ether (50ml). The mixture was stirred at -70°C for 90 minutes. A solution of 2-[3-chloro-4-(4-chlorobenzoyl)-phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.0138 mol) in THF (100ml) was added dropwise. The mixture was allowed to warm to -40°C, then poured out into ice water, neutralized with HCl 3N and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (5.88g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3). The pure fractions were collected and the solvent was evaporated. The residue was taken up in CH_3CN and diethyl ether. The precipitate was filtered off and dried, yielding 1.36g (±)-2-[3-chloro[4-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione monohydrate (compound 120)..

b) n-Butyllithium, 1.6M (0.0203 mol) was added dropwise at -70°C under N_2 flow to a solution of 1-methyl-1*H*-imidazole (0.0203 mol) in THF (60ml). The mixture was stirred at -70°C for 40 minutes. Chlorotriethylsilane (0.203 mol) was added quickly and the mixture was allowed to warm to 0°C on an ice bath. The mixture was cooled to -70°C and n-butyllithium (0.0203 mol) was added dropwise. The mixture was allowed to

warm to -20°C and cooled to -70°C. A solution of 2-[3-chloro-4-(4-chlorobenzoyl)-phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.00812 mol) in THF (20ml) was added dropwise. The mixture was allowed to warm to -5°C, then poured out into a satured NH_4Cl solution and ice, and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 96/4). The pure fractions were collected and the solvent was evaporated. The residue (0.85g) was crystallized from 2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 0.47g (13%) of (±)-2-[3-chloro-4-[(chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione monohydrate (compound 121).

c) n-Butyllithium (0.1 mol) was added dropwise at -70°C under N_2 flow to a solution of *N,N*-dimethylethanamine (0.1 mol) in THF (100ml). The mixture was stirred at -20°C for 30 minutes and cooled again to -70°C. Acetonitrile (0.1 mol) was added dropwise. The mixture was stirred at -20°C for 1 hour and cooled again to -70°C. A solution of 2-[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.05 mol) in THF (100ml) was added dropwise. The mixture was stirred at -70°C for 1 hour, then poured out into NH_4Cl 10% and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 98/2). Two pure fractions were collected and their solvents were evaporated, yielding 1.62g (8%) of (±)-2,6-dichloro-α-(4-chlorophenyl)-4-[4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl]-α-hydroxybenzenepropanenitrile (compound 122).

Example B5

a) A mixture of intermediate (25) (0.0289 mol) in 2-mercaptoacetic acid (15ml) was stirred at 150°C for 3 hours and then cooled. The mixture was poured out in water, neutralized, and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. A sample of this product was crystallized from 2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 1.2g (±)-2-[3-chloro-4-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 123)..

b) (±)-2-[3-chloro-4-[(4-chlorophenyl)-3-pyridinylmethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione was prepared according to the procedure described in example B5a but using 1,2-dimethoxyethane instead of 2-mercaptoacetic acid (compound 124).

Example B6

a) A mixture of intermediate (50) (0.0027 mol) in toluene (100ml) was stirred and refluxed using a Dean-Stark apparatus. The mixture was decanted and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether.. The precipitate was filtered off and dried, yielding 1.04g (78%) (±)-2-[(3-chloro-4-[(4-chlorophenyl)(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4 *H*)-dione (compound 125).

b) (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]phenyl]-1,2,4-triazin-3,5(2*H*,4*H*)-dione (comp. 429; mp. 128°C) was prepared analogous to the procedure described in example B6.a except that the starting product was mixed with *p*-toluenesulfonic acid and dimethylsulfoxide instead of toluene.

Example B7

A mixture of intermediate (66) (0.022 mol) and sodium methoxide, 30% in methanol (0.033 mol) in 1-butanol (350ml) was stirred at RT for 30 minutes. Molecular sieves (12.6g) and then EtOAc (0.033 mol) were added. The mixture was stirred and refluxed overnight, filtered over celite and the solvent was evaporated. The residue was taken up in CH_2Cl_2, washed with HCl 3N and then with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone and DIPE. The precipitate was filtered off and dried, yielding 2.1g (±)-2-[3-chloro-4-[(4-chlorophenyl)(5-methyl-1,2,4-oxadiazol-3-yl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 126).

Example B8

a) Intermediate (54) (0.00294 mol) was added portionwise at 5°C to phosphoryl chloride (15ml). The mixture was allowed to warm to RT, then stirred at 80°C overnight and cooled. The solvent was evaporated. Ice water was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97.5/2.5). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 0.5g (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)(5-phenyl-1,3,4-oxadizol-2-yl)methyl]-phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 127).

b) Compound 127 (0.0114 mol) was dissolved in hexane/ethanol/methanol 50/25/25

(400 ml), then separated into its enantiomers by chiral column chromatography over a Chiralpak AS column (230 g, 20 µm, I.D.: 5 cm; eluent: hexane/ethanol + 0.1% CF_3COOH/methanol 66/17/17). Two fraction groups were collected. Fraction 1 was added to water. The organic solvent was evaporated and the aqueous concentrate was extracted with CH_2Cl_2. The solvent of the separated organic phase was evaporated. Fraction 2 was treated analogously. Both residues, each individually, were post-purified over Lichroprep 200 (eluent gradient: CH_2Cl_2/CH_3OH). Two pure fraction groups were collected and the solvent was evaporated, yielding 2.86 g (A)-2-[3,5-dichloro-4-[(4-chlorophenyl)(5-phenyl-1,3,4-oxadizol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 189; α^D_{20} = +50.98° (c = 24.42 mg/5 ml in CH_3OH)) and 1.75 g (B)-2-[3,5-dichloro-4-[(4-chlorophenyl)(5-phenyl-1,3,4-oxadizol-2-yl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 190; α^D_{20} = -50.83° (c = 22.92 mg/5 ml in CH_3OH)).

Example B9

A mixture of intermediate (59) (0.0108 mol) in toluene (120ml) and methanesulfonic acid (1.05ml) was stirred and refluxed for 4 hours, cooled, poured out into water, decanted, and basified to pH=8 with NH_4OH, while stirring. The aqueous layer was neutralized and extracted with CH_2Cl_2. The organic layer was washed with water, dried, filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The desired fractions were collected and the solvent was evaporated. The residue was repurified by HPLC (eluent: CH_3OH/H_2O 80/20). Two pure fractions were collected and their solvents were evaporated, yielding 0.44g (8%) of (±)-2-[3-chloro-4-[(4-chlorophenyl)-[5-(phenylamino)-1,3,4-thiadizol-2-yl]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 129), and 0.27g (5%) of (±)-2-[3-chloro-4-[(4-chlorophenyl) (4,5-dihydro-4-phenyl-5-thioxo-1*H*-1,2,4-triazol-3-yl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 128)

Example B10

a) A mixture of intermediate (65) (0.00275 mol) and triethylamine (0.003 mol) in THF (20ml) was stirred at RT. Benzoyl chloride (0.00275 mol) in THF (10ml) was added dropwise and the reaction mixture was stirred at RT for 3 hours. The solvent was evaporated. The residue was stirred in H_2O and CH_2Cl_2. The organic layer was dried, filtered, and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 98/2). The desired fractions were collected and the solvent was evaporated. The residue was repurified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The desired fractions were collected and the

solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE and dried. The residue was repurified by HPLC over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried, yielding 0.4 g (±)-*N*-[[2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-3(2*H*)-yl)phenyl](4-chlorophenyl)methyl]benzamide (compound 47).

b) A mixture of intermediate 65 (0.00275 mol) and 2-methylthiothiazolo[5,4-b]pyridine (0.0035 mol) was heated up to 170 °C and stirred for 2 days. The reaction mixture was dissolved in CH_2Cl_2/CH_3OH (90/10). The precipitate was filtered off and the filtrate was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried, yielding 0.1 g of (±)-2-[3-chloro-4-[(4-chlorophenyl)[(thiazolo[5,4-b]pyridin-2-yl)-amino]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione. (comp. 410)

Example B11

A solution of intermediate (63) (0.0080 mol), 6-chloro-2,4-dimethoxypyrimidine (0.0084 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0088 mol) in DMF (50 ml) was stirred for 4 days at RT. The solvent was evaporated and the residue was stirred in water and this mixture was extracted with CH_2Cl_2/CH_3OH 90/10. The separated organic layer was dried, filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The desired fractions were collected and the solvent was evaporated. The residue was repurified by reversed-phase liquid chromatography over silica gel (eluent: (0.5% NH_4OAc in H_2O)/CH_3OH/CH_3CN 28/36/36, upgrading to 0/50/50). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed, then dried, yielding 0.4 g (±)-2-[3-chloro-4-[(4-chloro-phenyl)[(2,6-dimethoxy-2-pyrimidinyl)thio]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 96).

Example B12

A solution of intermediate (48) (0.012 mol) in pyridine (45ml) was added to a solution of 2-mercapto-2-benzenamine (0.0132 mol) in pyridine (30ml). The mixture was stirred and heated at 60°C for 18 hours, poured out into HCl 3N, and extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The pure fractions were collected and the solvent was

evaporated, yielding 1.23g (21%) (±)-2-[4-[2-benzothiazolyl-(4-chlorophenyl)methyl]-3-chlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 130).

Example B13

a) A mixture of 2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneethanethionate (0.00453 mol) and 2-bromo-1-phenylethanone (0.00498 mol) in ethanol (80ml) was stirred and refluxed for 2 hours. The solvent was evaporated. The residue was taken up in CH_2Cl_2, washed with K_2CO_3 10% and then with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/0.5;). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 1.05g (43%) of (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)(4-phenyl-2-thiazolyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 38).

b) (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)[5-(1-methylethyl)-4-phenyl-2-thiazolyl]methyl]-phenyl]-1,2,4-triazin-3,5(2*H*,4*H*)-dione (comp. 241) was prepared according to example B13.a and in addition triethylamine was used as a base.

c) 2,6-Dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneethanethioamide (0.031 mol) was added at RT to a solution of (±)-1,1-dimethylethyl α-bromo-β-oxo-benzenepropanoate (0.0465 mol) and K_2CO_3 (0.093 mol) in CH_3CN (190ml). The mixture was stirred at RT for 3.5 hours. H_2O was added. The mixture was acidified with HCl 3N and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The pure fractions were collected and the solvent was evaporated, yielding 11g (54%) of (±)-1,1-dimethylethyl 2-[(4-chlorophenyl)[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]methyl]-4-phenyl-5-thiazolcarboxylate (comp. 298).

Example B14

A mixture of 2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneethanethionate (0.0197 mol) and 1-bromo-2,2-diethoxyethane (0.0256 mol) in HCl 3N (10ml) and ethanol (145ml) was stirred and refluxed for 5 hours. The solvent was evaporated. The residue was taken up in CH_2Cl_2, washed with K_2CO_3 10% and extracted with CH_2Cl_2. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/15/1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off, dried and recrystallized from

2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 1.32g (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)-2-thiazolylmethyl]-phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 39).

Example B15

a) A mixture of intermediate (52) (0.0076 mol) in EtOAc (45ml) was stirred and refluxed for 18 hours, then poured out into H_2O and extracted with EtOAc. The organic layer was separated, washed with K_2CO_3 10% and with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The pure fractions were collected and the solvent was evaporated, yielding 0.9g (25%) of (±)-2-[4-[2-benzoxazolyl(4-chlorophenyl)methyl]-3-chlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 131).
b) (±)-2-[3-chloro-4-[1-(4-chlorophenyl)-1-(2-benzoxazolyl)ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione was prepared using the same procedure as in example B15a but by using methanesulfonic acid instead of acetic acid (compound 132).

Example B16

A mixture of compound (33) (0.0231 mol) in methanol (100ml) and sulfonic acid (2ml) was stirred and refluxed for 3 days, then cooled, poured out on ice, neutralized and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1 to 98/2). The pure fractions were collected and the solvent was evaporated, yielding 4 g (38%) of (±)-2-[3-chloro-4-[(4-chlorophenyl)-methoxy(2-thiazolyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 37).

Example B17

a) Compound (33) (0.00425 mol) was dissolved in thionyl chloride (20ml) at 10°C, and the mixture was stirred at RT for 4 hours. The solvent was evaporated, yielding (±)-2-[3-chloro-4-[chloro(4-chlorophenyl)-2-thiazolylmethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 36).
b) A solution of compound (36) (0.00425 mol) in THF (20ml) was added dropwise at 5°C to NH_4OH (20ml) and the mixture was stirred at RT for 2 hours, then poured out on ice, neutralized with HCl 6N and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3). The pure fractions were collected and the solvent was evaporated. The residue was repurified by column chromatography over Kromasil C18 (eluent: $CH_3OH/H_2O/HOAc$ 70/30/1). The pure fractions were collected and the solvent was evaporated. The residue was taken up in H_2O and NH_4OH (pH=8) was added. The precipitate was filtered off, washed with

H_2O and diethyl ether, and dried, yielding 0.3g (±)-2-[3-chloro-4-[amino-(4-chlorophenyl)-2-thiazolylmethyl] phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (compound 35).

Example B.18

A mixture of 2-[3,5-dichloro-4-[(4-chlorophenyl)hydroxymethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.005 mol) and 5-phenyl-1,3,4-oxadiazole-2(3*H*)-thione (0.006 mol) in methanesulfonic acid (20 ml) was stirred for 18 hours at RT. The reaction mixture was poured out into water/ice (150 ml), and the resulting precipitate was filtered off, stirred in water, treated with $NaHCO_3$ and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97.5/2.5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried, yielding 1 g of (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 406).

Example B.19

a) A solution of 2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetyl chloride (0.188 mol) in 1,4-dioxane (900 ml) was stirred at RT. $NaBH_4$ (36.25 g) was added portionwise over 2.5 hours. The resulting reaction mixture was stirred for 3 hours at RT. The reaction mixture was cooled and acidified till pH 6 with 1 N HCl. The precipitated salts were removed by filtration. The filtrate was washed with water, and the precipitate was filtered off, stirred in DIPE, filtered off and dried, yielding 22.5 g of (±)-2-[3,5-dichloro-4-[1-(4-chlorophenyl)-2-hydroxyethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 420). The biphasic filtrate was separated into its layers. The organic layer was dried, filtered and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5 and 97/3). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed, and dried, yielding 24 g of (±)-2-[3,5-dichloro-4-[1-(4-chlorophenyl)-2-hydroxyethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 420).

b) A solution of compound 420 (0.01 mol) and *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.02 mol) in 1,4-dioxane (80 ml) was stirred at 5-10°C under N_2 atmosphere. A solution of methanesulfonyl chloride (0.02 mol) in 1,4-dioxane(10 ml) was added dropwise at 5-10 °C. The resulting reaction mixture was stirred for one hour at RT. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water, dried, filtered and the solvent was evaporated, yielding 4.9 g of (±)-2-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]-2-(4-chlorophenyl)ethanol methanesulfonate (ester) (comp. 435).

c) A mixture of compound 435 (0.001 mol), 2-pyridinethiol (0.0012 mol) and $NaHCO_3$ (0.0012 mol) in DMF (30ml) was stirred at RT under N_2 flow, then heated to 60°C and stirred for 48 hours. 2-pyridinethiol (0.0012 mol) and $NaHCO_3$ (0.0012 mol) were added again. The mixture was stirred for 1 day. 2-pyridinethiol (0.006 mol) was added again and the mixture was stirred and refluxed for 1 day. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and extracted with water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by HPLC (eluent: NH_4OAc 0.5% in $H_2O/CH_3OH/CH_3CN$ 67.5/ 7.5/25 to 0/50/50 after 10 minutes to 0/0/100 after 10 minutes). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried, yielding 0.05g (10%) of (±)-2-[3,5-di-chloro-4-[1-(4-chlorophenyl)-2-(2-pyridinylthio)ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 422).

Example B.20

A mixture of intermediate 75 (0.0159 mol) in dimethylsufoxide (170ml) and H_2O (20ml) was stirred at 160°C for 3 hours. The mixture was cooled and poured out on ice. The precipitate was filtered off, washed with H_2O and taken up in EtOAc. The organic solution was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.5/0.5 to 96/4). The desired fraction was collected and the solvent was evaporated, yielding 2015g of (±)-2-[3-chloro-4-[(4-chlorophenyl)(4-phenyl-2-thiazolyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 419; mp. 90°C).

Example B.21

A mixture of (±)-2-[4-[3-bromo-1-(4-chlorophenyl)-2-oxopropyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (0.0025 mol) and benzenecarbothioamide (0.0025 mol) in ethanol (25 ml) was stirred and refluxed for 3 hours, then stirred overnight at RT. The solvent was evaporated. The residue was purified twice by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH (1) 97/3 and (2) 98/2 v/v). The desired fractions were collected and the solvent was evaporated. The residue was repurified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The pure fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off, then dried, yielding 0.3 g (22%) of (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)(2-phenyl-4-thiazolyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 363).

Example B.22

a) Compound 298 (0.0137 mol) was added at 10°C under N_2 flow to trifluoroacetic acid (120ml). The mixture was allowed to warm to RT and stirred for 1 hour. H_2O was

added. The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2 and a small amount of CH_3OH. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/HOAc$ 97/3/0.1). The pure fractions were collected and the solvent was evaporated. This fraction was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 1.34g (67%) of (±)-2-[(4-chlorophenyl)[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]-methyl]-4-phenyl-5-thiazolcarboxylic acid (Comp. 299; mp 206°C).

b) 1,1'-Carbonylbis-1*H*-imidazole (0.0081 mol) was added to a suspension of compound 299 (0.00324 mol) in CH_2Cl_2 (25ml). The mixture was stirred at RT for 2 hours. Dimethylamine (0.00324 mol) was added. The mixture was stirred at RT for 48 hours. H_2O was added. The mixture was acidified with HCl 3N and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 1.04g (52%) of (±)-*N,N*-dimethyl-2-[(4-chlorophenyl)[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]methyl]-4-phenylthiazol-5-carboxamide (Comp. 303; mp 150°C).

Example B.23

a) A solution of compound 350 (0.014 mol) in 2,6-dimethylpyridine (1.63 ml) and THF (80 ml) was stirred and cooled to -78 °C. Trifluoromethanesulfonic anhydride (0.014 mol) was added dropwise and the mixture was stirred for 7 hours at -78 °C, yielding (±)-2-[[(4-chlorophenyl)[2,6-dichloro-4-(4,5-dihycro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]methyl]thio]-4-pyrimidinol trifluoromethanesulfonate (ester) (comp. 356).

b) A mixture of compound 356 (0.0047 mol) in THF (35 ml) was stirred at RT. 2-Aminoethanol (0.0235 mol) was added. The reaction mixture was stirred for one hour at 50 °C, then for 16 hours at RT. The solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1, 98/2 and 93/7). The desired fractions were collected and the solvent was evaporated. The residue was repurified by HPLC over silica gel (eluent: CH_2Cl_2/CH_3OH from 100/0 over 30 minutes to 92/8). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried, yielding 0.3 g of (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)[[4-[(2-hydroxyethyl)amino]-2-pyrimidinyl]-thio]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 357).

Example B.24

a) LiCl (0.035 mol) was added portionwise at 80°C to a mixture of compound 285 (0.007 mol) and KBH_4 (0.035 mol) in THF (45ml). The mixture was stirred at 80°C for 4 hours. KBH_4 (0.035 mol) and then LiCl (0.035 mol) were added. The mixture was stirred at 80°C for 4 hours, at RT overnight, then poured out into ice water, acidified with HCl 3N and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3; 20-45 μm). The pure fractions were collected and the solvent was evaporated, yielding 2.1g (51%) of (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)[4-(2-fluorophenyl)-5-(hydroxymethyl)-2-thiazolyl]methyl]phenyl]-1,2,4-triazin-3,5(2*H*,4*H*)-dione (comp. 323).

b) Thionylchloride (0.0113 mol) was added at 10°C to a mixture of compound 323 (0.0094 mol) in CH_2Cl_2 (30 ml). The mixture was stirred at RT for 2.5 hours, washed with H_2O and with K_2CO_3 10%, dried, filtered and the solvent was evaporated, yielding 2g of (±)-2-[4-[[5-(chloromethyl)-4-(2-fluorophenyl)-2-thiazolyl](4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 324).

c) A mixture of compound 324 (0.0034 mol), dimethylamine (0.0068 mol) and K_2CO_3 (0.0102 mol) in CH_3CN (100ml) was stirred and refluxed for 3 hours and then cooled. The solvent was evaporated. The residue was taken up in CH_2Cl_2. The organic solution was washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/H_2O$ 97/3/0.4). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether and CH_3CN. The precipitate was filtered off and dried, yielding 0.84g of (±)-2-[4-[(4-chlorophenyl)[5-[(dimethylamino)methyl]-4-(2-fluorophenyl)-2-thiazolyl]methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 325; mp 250°C).

Example B.25

A mixture of compound 229 (0.0041 mol) and triethylamine (0.0082 mol) in CH_2Cl_2 (45ml) was stirred at RT for 1 hour. A solution of acetyl chloride (0.0041 mol) in CH_2Cl_2 (5ml) was added at 10°C. The mixture was stirred at RT for 12 hours, then poured out into H_2O and decanted. The organic layer was washed with HCl 3N and with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN and DIPE. The precipitate was filtered off and dried, yielding 0.52g of (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)[4-(4-piperidinyl)-2-thiazolyl]methyl]phenyl]-1,2,4-triazine-3,5-(2*H*,4*H*)-dione monohydrochloride (comp. 230; mp 212°C).

Example B.26

A mixture of compound 212 (0.00646 mol) in NH_3/CH_3OH 7N (100ml) was stirred and refluxed for 3 hours and then cooled. The solvent was evaporated. The residue was taken up in EtOAc and a small amount of CH_3OH. The organic layer was separated, washed with HCl 3N, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 0.85g of (±)-*N*-[2-[5-[(4-chlorophenyl)[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]methyl]-1,3,4-oxodiazol-2-yl]phenyl]-2-hydroxyacetamide (comp. 213; mp 235°C).

Example B.27

A mixture of compound 352 (0.005 mol) in HBr (75 ml; 48%) was stirred at RT. The mixture was warmed to 140°C on an oil bath and stirred for 30 minutes. The mixture was cooled. The solvent was evaporated. H_2O was added. The mixture was neutralized with NaOH 50% and extracted with CH_2Cl_2. The product was filtered off and stirred in CH_3OH, in CH_3CN and then in CH_2Cl_2, and dried. This fraction was stirred in H_2O (20 ml), and CH_3COOH (±1 equiv) was addded. The product was filtered off, washed with H_2O and dried, yielding 1.3 g of (±)-2-[3,5-dichloro-4-[(4-chlorophenyl)[[4-(1-piperazinyl)-2-pyrimidinyl]thio]methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione monohydrate (comp. 360).

Example B.28

a) A mixture of compound 192 (0.014 mol) in THF (100 ml) and methanol (100 ml) was hydrogenated at 50°C with platina on activated charcoal (2 g; 10%) as a catalyst in the presence of a thiophene solution (2 ml). After uptake of H_2, the catalyst was filtered off and the filtrate was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 6.2 g of (±)-2-[4-[[5-(3-aminophenyl)-1,3,4-oxadiazol-2-yl](4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (comp. 193).

b) Compound 193 (0.012 mol) was dissolved in acetic acid (40 ml) and HCl (3.6 ml) at about 5°C. A solution of $NaNO_2$ (0.0126 mol) in H_2O (10 ml) was added dropwise at 5°C. The reaction mixture was stirred for 1 hour at 5 °C. NaN_3 (0.0126 mol) was added portionwise. The reaction mixture was stirred for 30 minutes, then poured out onto ice. The precipitate was filtered off, washed with water, then dissolved in CH_2Cl_2. The organic solution was dried, filtered, and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling ethanol, filtered off and washed with ethanol/DIPE, then dried, yielding 2.1 g of (±)-2-[4-[[5-(3-azidophenyl)-1,3,4-oxadiazol-2-yl](4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-

triazine-3,5(*2H,4H*)-dione (comp. 194).

Example B.29

a) A mixture of compound 328 (0.00271 mol) in HBr (20ml; 33% in HOAc) and HBr (20ml; 48% in H_2O) was stirred and refluxed overnight, then cooled, poured out into ice water, neutralized with a concentrated NaOH solution and centrifuged. The residue was washed with H_2O and dried. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was taken up in CH_3OH and CH_2Cl_2. The organic solution was washed with a solution at pH 4 and a solution at pH 7, then dried. Activated charcoal was added. The mixture was filtered over celite. The solvent was evaporated. The residue was crystallized from CH_3CN and diethyl ether. The precipitate was filtered off and dried, yielding 0.27g of (±)-2-[4-[[5-(aminomethyl)-4-phenyl-2-thiazolyl](4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(*2H,4H*)-dione (comp. 329; mp 170°C).

b) A solution of compound 329 (0.0035 mol) and isothiocyanatobenzene (0.0042 mol) in THF (25ml) was stirred at RT for 90 minutes. The solvent was evaporated. The residue was dissolved in CH_2Cl_2. The organic solution was washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried, yielding 0.64g (±)-*N*-[[2-[(4-chlorophenyl)[2,6-dichloro-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(*3H*)-yl)phenyl]methyl]-4-phenyl-5-thiazolyl]methyl]-*N'*-phenyl-thiourea (comp. 331; mp 159°C).

Example B.30

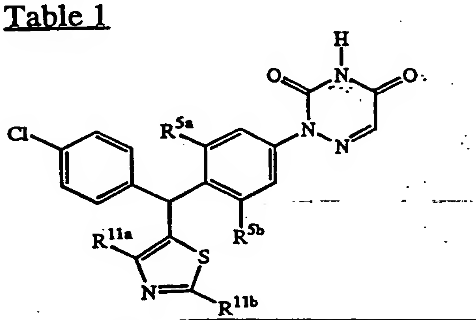
a) $TiCl_3$ (0.034 mol; 15% aqueous solution) was added dropwise at RT to a mixture of compound 216 (0.0034 mol) in THF (60ml). The mixture was stirred at RT for 5 hours, poured out into H_2O and extracted with EtOAc. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated, yielding 1.9g of (±)-2-[4-[[5-(3-amino-2-methylphenyl)-1,3,4-oxadiazol-2-yl](4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(*2H,4H*)-dione (comp. 217).

b) A mixture of (acetyloxy)acetyl chloride (0.0121 mol) in CH_2Cl_2 (15ml) was added at 10°C under N_2 flow to a mixture of compound 217 (0.011 mol) and *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.0165 mol) in CH_2Cl_2 (60 ml). The mixture was stirred at RT for 12 hours, poured out into H_2O, acidified with HCl 3N and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3). The pure fractions were collected and the solvent was

evaporated. Part of the residue (0.9g) was crystallized from diethyl ether and CH_3CN. The precipitate was filtered off and dried, yielding 0.65g of (±)-2-(acetyloxy)-*N*-[3-[5-[(4-chlorophenyl)[2,6-dichloro-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)yl)phenyl]methyl]-1,3,4-oxadiazol-2-yl]-2-methylphenyl]acetamide. (comp. 223; mp 206°C).

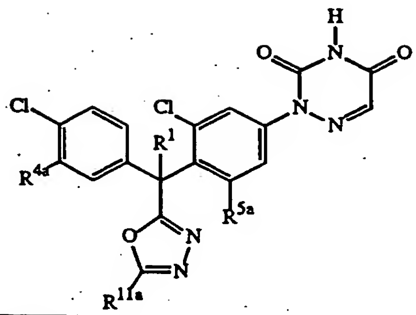
Tables 1 to 8 list compounds of the present invention as prepared according to one of the above examples. These all are racemic mixtures unless otherwise mentioned.

Table 1



Co. No.	Ex. No.	R^{5a}	R^{5b}	R^{11a}	R^{11b}	Melting-point °C
134	B5a	Cl	H	phenyl	CH3	180°C
135	B5a	Cl	Cl	2-Cl-phenyl	CH3	170°C
136	B5a	Cl	Cl	phenyl	CH_3	175°C
137	B5a	Cl	Cl	CH_3	2-Cl-phenyl	120°C
138	B5a	Cl	Cl	CH_3	phenyl	120°C
139	B5a	Cl	H	2-Cl-phenyl	CH_3	>260°C
140	B5a	Cl	H	phenyl	phenyl	186-188°C
141	B5a	Cl	H	H	phenyl	168°C
142	B5a	Cl	Cl	H	phenyl	
143	B5a	Cl	H	3-F-phenyl	CH_3	146°C
144	B5a	H	Cl	2-Cl-phenyl	phenyl	140°C
145	B5a	Cl	Cl	2-Cl-phenyl	phenyl	160°C
146	B5a	H	H	phenyl	CH_3	230°C
147	B5a	Cl	Cl	2-Cl-phenyl	2-Cl-phenyl	158°C
148	B5a	Cl	H	3-F-phenyl	H	155°C
149	B5a	Cl	H	4-Cl-phenyl	CH_3	145°C
150	B5a	Cl	H	phenyl	2-Cl-phenyl	220°C
151	B5a	Cl	H	2-Cl-phenyl	2-Cl-phenyl	150°C
152	B5a	Cl	Cl	2-F-phenyl	CH_3	185°C
153	B5a	H	OCH_3	phenyl	CH_3	163°C
154	B5a	Cl	H	CH_3	2-Cl-phenyl	190°C

Table 2



Co. No.	Ex. No.	R^1	R^{4a}	R^{5a}	R^{11a}	salt form / stereochemistry/ melting point
155	B8a	CH_3	CF_3	H	phenyl	126°C
156	B8a	H	H	Cl	2-F-phenyl	169°C
157	B8a	H	H	Cl	3-Cl-phenyl	188°C
158	B8a	H	H	Cl	4-pyridinyl	H_2O (1:1)/170°C
159	B8a	H	H	Cl	cyclohexyl	164°C
160	B8a	H	H	Cl	3-F-phenyl	156°C
161	B8a	H	H	Cl	2-furanyl	170°C
162	B8a	H	H	Cl	methyl	120°C
163	B8a	H	H	Cl	2-Cl-phenyl	H_2O (1:1)/160°C
164	B8a	H	H	Cl	propyl	135°C
165	B8a	H	CF_3	Cl	phenyl	212°C
166	B8a	H	H	Cl	2-thienyl	180°C
167	B8a	H	H	Cl	4-Cl-phenyl	230°C
168	B8a	H	H	Cl	4-Br-phenyl	
169	B8a	H	H	Cl	2-pyridinyl	182°C
170	B8a	H	H	Cl	3-methoxyphenyl	208°C
171	B8a	H	H	Cl	4-methoxyphenyl	212°C
172	B8a	H	H	Cl	phenylethyl	148°C
173	B8a	H	H	Cl	phenyl-CH_2-	190°C
174	B8a	H	H	Cl	2-(methoxy)phenyl	164°C
175	B8a	H	H	Cl	(2-Cl-phenyl)-O-CH_2-	135°C
176	B8a	H	H	Cl	C_2H_5-O-CO-CH_2-	177°C
177	B8a	H	H	Cl	4-CH_3-phenyl	>260°C
178	B8a	H	H	Cl	3-CH_3-phenyl	188°C
179	B8a	H	H	Cl	NC-CH_2-	222°C
180	B8a	H	H	Cl	4-[$N(CH_3)_2$]-phenyl	224°C
181	B8a	H	H	Cl	C_2H_5-O-$(CH_2)_2$-	130°C
182	B8a	H	H	Cl	3-[$N(CH_3)_2$]-phenyl	240°C
183	B2a	H	H	Cl	4-nitrophenyl	
184	B28	H	H	Cl	4-aminophenyl	
185	B28b	H	H	Cl	4-(-N=N^+=N^-)-phenyl	
186	B8a	H	H	Cl	C_2H_5-O-CO-	137°C
187	B8a	H	H	Cl	phenyl-O-$(CH_2)_2$-	215°C

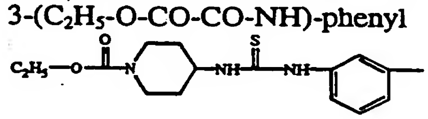
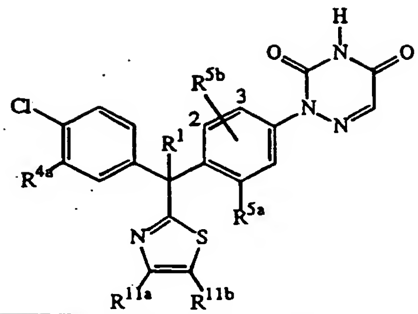
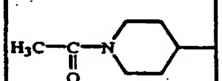
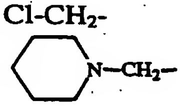
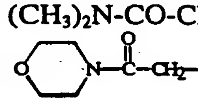
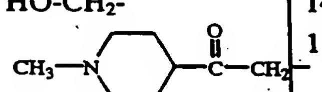
Co. No.	Ex. No.	R^1	R^{4a}	R^{5a}	R^{11a}	salt form / stereochemistry/ melting point
188	B8a	H	H	Cl	2-CH_3-phenyl	150°C
189	B8b	H	H	Cl	phenyl	(A)
190	B8b	H	H	Cl	phenyl	(B)
191	B8a	H	H	Cl	1-(C_2H_5-O-CO)-4-piperidinyl	230°C
192	B8a	H	H	Cl	3-nitrophenyl	
193	B28a	H	H	Cl	3-aminophenyl	
194	B28b	H	H	Cl	3-(-N=N^+=N^-)-phenyl	
195	B8a	H	H	Cl	1-CH_3-4-piperidinyl	
196	B8a	H	H	Cl	1-CH_3-3-piperidinyl	150°C
197	B8a	H	H	Cl	Cl-CH_2-	
198	B24c	H	H	Cl	$(CH_3)_2$-N-CH_2-	188°C
199	B8a	H	H	Cl	4-(4-CH_3-1-piperazinyl)phenyl	150°C
200	B8a	H	H	Cl	3-OH-phenyl	159°C
201	B8a	H	H	Cl	3-pyridinyl	190°C
202	B8a	H	H	Cl	2-hydroxyphenyl	180°C
203	B8a	H	H	Cl	3-CH_3-2-thienyl	161°C
204	B8a	H	H	Cl	3-(NH_2-SO_2)-phenyl	H_2O (1:1)/196°C
205	B8a	H	H	Cl	3-(CH_3-SO_2)-phenyl	185°C
206	B8a	CH_3	H	Cl	phenyl	180°C
207	B8a	H	H	Cl	3-CH_3-2-furanyl	188°C
208	B30b	H	H	Cl	3-(CH_3-SO_2-NH)-phenyl	>250°C
209	B8a	H	H	Cl	2-(CH_3-SO_2)	230°C
210	B8a	H	H	Cl	2-nitrophenyl	180°C
211	B30a	H	H	Cl	2-aminophenyl	
212	B30b	H	H	Cl	2-(CH_3-CO-O-CH_2-CO-NH)-phenyl	
213	B26	H	H	Cl	2-(HO-CH_2-CO-NH)-phenyl	235°C
214	B30b	H	H	Cl	3-(CH_3-CO-O-CH_2-CO-NH)-phenyl	
215	B26	H	H	Cl	3-(HO-CH_2-CO-NH)-phenyl	>250°C
216	B8a	H	H	Cl	2-CH_3-3-nitrophenyl	
217	B30a	H	H	Cl	3-amino-2-methylphenyl	
218	B30b	H	H	Cl	2-CH_3-3-(NH_2-SO_2-NH)-phenyl	180°C
219	B30b	H	H	Cl	3-(C_2H_5-O-CO-CO-NH)-phenyl	H_2O (1:1)/208°C
220	B29b	H	H	Cl		180°C
221	B30b	H	H	Cl	3-(NH_2-SO_2-NH)-phenyl	H_2O (1:1)/220°C
222	B8a	H	H	Cl	2-CH_3-3-pyridinyl	160°C
223	B30b	H	H	Cl	2-CH_3-3-(CH_3-CO-O-CH_2-CO-NH)-phenyl	206°C

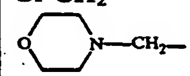
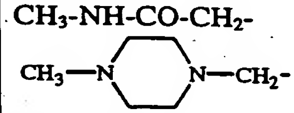
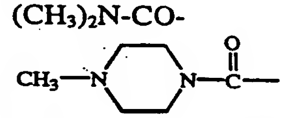
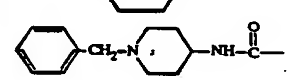
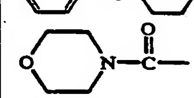
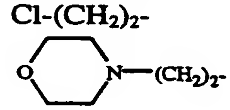
Table 3

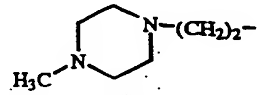
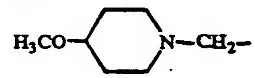
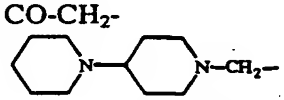
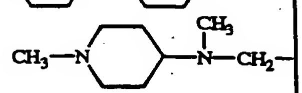
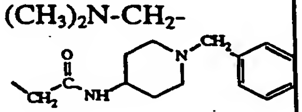
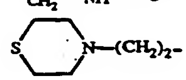
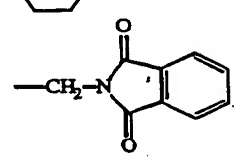


Co. No.	Ex. No.	R^1	R^{4a}	R^{5a}	R^{5b}	R^{11a}	R^{11b}	Salt form stereochem /mp.
1	B16	CH_3O	H	Cl	H	phenyl	H	126°C
2	B14	H	H	Cl	H	H	H	
3	B14	CH_3	H	Cl	H	H	H	
4	B13a	H	H	Cl	H	phenyl	H	
5	B13a	H	H	Cl	H	4-pyridinyl	H	HBr (1:1)/ H_2O (1:1)
6	B13a	H	H	Cl	2-Cl	phenyl	phenyl	
7	B13a	H	H	Cl	2-Cl	phenyl	CH_3	
8	B13a	CH_3	H	Cl	2-Cl	phenyl	H	110°C
9	B13a	H	H	Cl	2-Cl	4-Cl-phenyl	H	
10	B13a	H	H	Cl	H	CH_3	H	
11	B13a	H	H	Cl	H	phenyl	phenyl	
12	B13a	CH_3	H	Cl	H	phenyl	H	
13	B13a	H	H	Cl	H	4-Cl-phenyl	H	
14	B13a	H	H	Cl	2-Cl	CH_3	H	
15	B13a	H	H	Cl	2-Cl	4-pyridinyl	H	
16	B13a	H	H	Cl	2-Cl	CH_3	CH_3	
17	B13a	H	H	Cl	2-Cl	4-[$N(C_2H_5)$]-phenyl	H	
18	B13a	CH_3	H	Cl	2-Cl	phenyl	phenyl	
19	B13a	H	H	Cl	2-Cl	3-Cl-phenyl	H	148°C
20	B13a	H	H	Cl	2-Cl	3-CF_3-phenyl	H	155°C
21	B13a	H	H	Cl	2-Cl	3-F-phenyl	H	167°C
22	B13a	H	H	Cl	2-Cl	3-CH_3-phenyl	H	162°C
23	B13a	CH_3	CF_3	Cl	2-Cl	phenyl	H	130°C
24	B13a	H	H	Cl	2-Cl	3-OCH_3-phenyl	H	130°C
25	B13a	H	H	Cl	2-Cl	2-Br-5-OCH_3-phenyl	H	130°C
26	B13a	H	H	Cl	2-Cl	4-OH-phenyl	H	255°C
27	B13a	H	H	Cl	2-Cl	C_2H_5O-CO-	H	220°C
28	B13a	H	H	Cl	2-Cl	3,4-diCl-phenyl	H	170°C
29	B13a	H	H	Cl	2-Cl	phenyl	C_2H_5O-CO-	144°C

Co. No.	Ex. No.	R^1	R^{4a}	R^{5a}	R^{5b}	R^{11a}	R^{11b}	Salt form stereochem /mp.
30	B13a	H	H	Cl	2-Cl	4-phenyl-phenyl	H	205°C
31	B13a	H	H	Cl	2-Cl	2-thienyl	H	164°C
32	B13a	H	H	Cl	2-Cl	2-Cl-phenyl	H	110°C
33	B4a	OH	H	Cl	H	H	H	
34	B4a	OH	H	Cl	H	phenyl	H	141°C
35	B17b	NH_2	H	Cl	H	H	H	
36	B17b	Cl	H	Cl	H	H	H	
37	B16	CH_3O	H	Cl	H	H	H	
38	B13a	H	H	Cl	2-Cl	phenyl	H	
39	B14	H	H	Cl	2-Cl	H	H	
224	B13a	H	H	Cl	2-Cl	phenyl	ethyl	260°C
225	B13a	H	H	Cl	2-Cl	phenyl-CH_2-	H	135°C
226	B13a	H	CF_3	Cl	2-Cl	phenyl	H	175°C
227	B13a	CH_3	Cl	Cl	2-Cl	phenyl	H	120°C
228	B13a	CH_3	Cl	Cl	2-Cl	phenyl	phenyl	130°C
229	B13a	H	H	Cl	2-Cl	4-piperidinyl	H	HCl (1:1)/ 200-210°C
230	B25	H	H	Cl	2-Cl		H	212°C
231	B13a	H	H	Cl	2-Cl	Cl-CH_2-	H	
232	B24c	H	H	Cl	2-Cl		H	175°C
233	B13a	CH_3	Cl	Cl	2-Cl	phenyl	CH_3	130°C
234	B13a	CH_3	CF_3	Cl	2-Cl	phenyl	CH_3	110°C
235	B13a	CH_3	CF_3	Cl	3-CH_3	phenyl	H	188°C
236	B13a	H	H	Cl	2-Cl	2-furanyl	H	126°C
237	B13a	CH_3	CF_3	Cl	2-Cl	phenyl	phenyl	120°C
238	B13a	CH_3	CF_3	Cl	3-CH_3	phenyl	CH_3	130°C
239	B13a	CH_3	CF_3	Cl	H	phenyl	H	126°C
240	B24c	H	H	Cl	2-Cl	$(CH_3)_2N$-CH_2-	H	226°C
241	B13b	H	H	Cl	2-Cl	phenyl	$(CH_3)_2CH$-	250°C
242	B13a	H	H	Cl	2-Cl	2-F-phenyl	H	85°C
243	B13a	H	H	Cl	2-Cl	2-CH_3-phenyl	H	92°C
244	B13a	H	H	Cl	2-Cl	2-Br-phenyl	H	90°C
245	B13a	H	H	Cl	2-Cl	phenyl	propyl	246°C
246	B13a	H	CF_3	Cl	2-Cl	phenyl	CH_3	180°C
247	B13a	CH_3	CH_3	Cl	H	phenyl	H	150°C

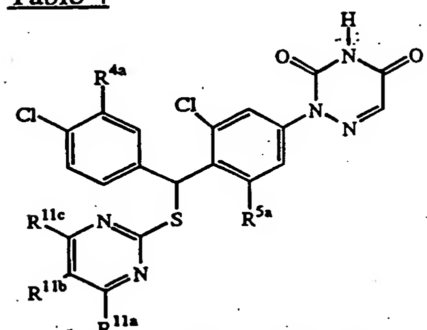
Co. No.	Ex. No.	R^1	R^{4a}	R^{5a}	R^{5b}	R^{11a}	R^{11b}	Salt form stereochem /mp.
248	B13a	H	H	Cl	2-Cl	CH_3	phenyl	146°C
249	B13a	H	H	Cl	2-Cl	phenyl	phenyl-CH_2-	176°C
250	B13a	H	H	Cl	2-Cl	3-Br-phenyl	H	116°C
251	B13a	CH_3	Cl	Cl	2-Cl	phenyl	ethyl	132°C
252	B13a	H	H	Cl	2-Cl	2,3-diCl-phenyl	H	98°C
253	B13a	H	H	Cl	2-Cl	phenyl	$(CH_3)_2N$-CH_2-	228°C
254	B13a	H	CF_3	Cl	2-Cl	2-Cl-phenyl	H	104°C
255	B13a	CH_3	CF_3	H	2-OCH_3	phenyl	H	89°C
256	B13a	H	H	Cl	2-Cl	phenyl	C_2H_5O-CO-CH_2-	170°C
257	B13a	H	H	Cl	2-Cl	2,5-diCl-phenyl	H	130°C
258	B13a	H	H	Cl	2-Cl	3-F-phenyl	CH_3	202°C
259	B13a	H	H	Cl	2-Cl	2-F-phenyl	CH_3	178°C
260	B13a	H	H	Cl	2-Cl	3-F-phenyl	ethyl	255°C
261	B13a	H	H	Cl	2-Cl	2-F-phenyl	ethyl	152°C
262	B13a	H	H	Cl	Cl	2-Cl-phenyl	ethyl	180°C
263	B13a	H	H	Cl	2-Cl	2-CH_3O-phenyl	H	120°C
264	B13a	H	H	Cl	2-Cl	2,6-diCl-phenyl	H	200°C
265	B17a	Cl	H	Cl	H	phenyl	Cl	
266	B3f	$(CH_3)_2N$-$(CH_2)_2$-NH-	H	Cl	H	phenyl	Cl	168°C
267	B13a	H	H	Cl	2-Cl	H	phenyl	175°C
268	B13a	H	H	Cl	2-Cl	2,6-diF-phenyl	CH_3	170°C
269	B13a	H	CH_3	Cl	2-Cl	phenyl	H	126°C
270	B13a	H	Cl	CH_3	2-CH_3	phenyl	H	181°C
271	B13a	H	Cl	CH_3	2-CH_3	phenyl	CH_3	140°C
272	B13a	H	H	Cl	2-Cl	2-Cl-phenyl	CH_3	182°C
273	B13a	H	H	Cl	2-Cl	phenyl	phenyl-CO-	148°C
274	B13a	H	H	Cl	2-Cl	2-Cl-phenyl	C_2H_5O-CO-	232°C
275	B13a	H	H	Cl	2-Cl	phenyl	$(CH_3)_2N$-CO-CH_2-	216°C
276	B13a	H	H	Cl	2-Cl	phenyl		203°C
277	B13a	H	H	Cl	2-Cl	phenyl	C_2H_5O-CO-$(CH_2)_2$-	184°C
278	B13c	H	H	Cl	2-Cl	phenyl	CH_3O-CH_2-	228°C
279	B13a	H	H	Cl	2-Cl	phenyl	$(CH_3)_2N$-$(CH_2)_2$-	229°C
280	B13a	H	H	Cl	2-Cl	3-F-phenyl	$(CH_3)_2N$-CH_2-	219°C
281	B13a	H	H	Cl	2-Cl	phenyl	$(CH_3)_2N$-CO-$(CH_2)_2$-	204°C
282	B24a	H	H	Cl	2-Cl	phenyl	HO-CH_2-	142°C
283	B13a	H	H	Cl	2-Cl	phenyl		160°C

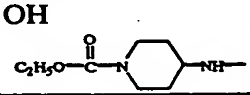
Co. No.	Ex. No.	R^1	R^{4a}	R^{5a}	R^{5b}	R^{11a}	R^{11b}	Salt form stereochem /mp.
284	B13a	H	H	Cl	2-Cl	phenyl	cyclohexyl	250°C
285	B13a	H	H	Cl	2-Cl	2-F-phenyl	C_2H_5O-CO-	222°C
286	B13a	H	H	Cl	2-Cl	3,5-diF-phenyl	H	125°C
287	B13a	H	H	Cl	2-Cl	3-F-phenyl	CH_3	95°C
288	B13a	CH_3	F	Cl	2-Cl	phenyl	H	100°C
289	B13a	H	OCH_3	Cl	2-Cl	phenyl	H	158°C
290	B13a	H	H	Cl	2-Cl	2,5-diF-phenyl	H	120°C
291	B24b	H	H	Cl	2-Cl	phenyl	Cl-CH_2-	
292	B24c	H	H	Cl	2-Cl	phenyl		105°C
293	B13a	H	H	Cl	2-Cl	2-Cl-phenyl	C_2H_5O-CO-CH_2-	174°C
294	B13a	H	H	Cl	2-Cl	4-Br-phenyl	H	
295	B13c	H	H	Cl	2-Cl	phenyl	C_2H_5-O-CH_2-	210°C
296	B24c	H	H	Cl	2-Cl	phenyl	CH_3-NH-CH_2-	HCl (1:1); H_2O (1:3)/ 205°C
297	B13a	H	H	Cl	2-Cl	phenyl	phenyl-CH_2-N(CH_3)-CH_2-	210°C
298	B13c	H	H	Cl	2-Cl	phenyl	$(CH_3)_3C$-O-CO-	
299	B22a	H	H	Cl	2-Cl	phenyl	HOOC-	206°C
300	B13a	H	H	Cl	2-Cl	phenyl	HOOC-CH_2-	186°C
301	B13c	H	H	Cl	2-Cl	phenyl	CH_3-NH-CO-CH_2-	158°C
302	B24c	H	H	Cl	2-Cl	phenyl		186°C
303	B22b	H	H	Cl	2-Cl	phenyl	$(CH_3)_2$N-CO-	150°C
304	B22b	H	H	Cl	2-Cl	phenyl		170°C
305	B22b	H	H	Cl	2-Cl	phenyl		210°C
306	B22b	H	H	Cl	2-Cl	phenyl		156°C
307	B22b	H	H	Cl	2-Cl	phenyl	CH_3O-$(CH_2)_2$-NH-CO-	248°C
308	B13a	H	H	Cl	2-Cl	phenyl	Cl-$(CH_2)_2$-	
309	B24c	H	H	Cl	2-Cl	phenyl		trifluoro acetate (1:1)
310	B13c	H	H	Cl	2-Cl	phenyl	c.C_6H_{11}-O-CH_2-	200°C
311	B24c	H	H	Cl	2-Cl	phenyl	$(CH_3)_2$N-$(CH_2)_2$-N(CH_3)-CH_2-	170°C

Co. No.	Ex. No.	R^1	R^{4a}	R^{5a}	R^{5b}	R^{11a}	R^{11b}	Salt form stereochem /mp.
312	B22b	H	H	Cl	2-Cl	phenyl	$(CH_3)_2N-(CH_2)_2-NH-CO-$	H_2O (1:1)/ 160°C
313	B24c	H	H	Cl	2-Cl	phenyl		H_2O (1:1)/ 216°C
314	B24c	H	H	Cl	2-Cl	phenyl		HCl (1:1)/H_2O (1:1)/190°C
315	B24c	H	H	Cl	2-Cl	phenyl	$CH_3O-CH(CH_3)-$	>260°C
316	B24c	H	H	Cl	2-Cl	phenyl	$CH_3O-(CH_2)_2-NH-CH_2-$	110°C
317	B22b	H	H	Cl	2-Cl	phenyl	$(CH_3)_2N-(CH_2)_2-NH-CO-CH_2-$	156°C
318	B13a	H	H	Cl	2-Cl	3-F-phenyl	H	(A)/120°C
319	B13a	H	H	Cl	2-Cl	3-F-phenyl	H	(B)/120°C
320	B22b	H	H	Cl	2-Cl	phenyl	$CH_3O-(CH_2)_2-NH-CO-CH_2-$	170-172°C
321	B24c	H	H	Cl	2-Cl	phenyl		210°C
322	B24c	H	H	Cl	2-Cl	phenyl		168°C
323	B24a	H	H	Cl	2-Cl	2-F-phenyl	$HO-CH_2-$	
324	B24b	H	H	Cl	2-Cl	2-F-phenyl	$Cl-CH_2-$	
325	B24c	H	H	Cl	2-Cl	2-F-phenyl	$(CH_3)_2N-CH_2-$	250°C
326	B22b	H	H	Cl	2-Cl	phenyl		140°C
327	B24c	H	H	Cl	2-Cl	phenyl		170°C
328	B13a	H	H	Cl	2-Cl	phenyl		
329	B29a	H	H	Cl	2-Cl	phenyl	NH_2-CH_2-	H_2O (1:1)/ 170°C
330	B13a	H	H	Br	2-Br	phenyl	CH_3	228°C
331	B29b	H	H	Cl	2-Cl	phenyl	phenyl-NH-C(=S)-NH-CH_2-	159°C
332	B24c	H	H	Cl	2-Cl	phenyl	phenyl-$(CH_2)_2$-N(CH_3)-CH_2-	187°C
333	B29b	H	H	Cl	2-Cl	phenyl	(4-Cl-phenyl)-NH-CO-NH-CH_2-	202°C

Co. No.	Ex. No.	R^1	R^{4a}	R^{5a}	R^{5b}	R^{11a}	R^{11b}	Salt form stereochem /mp.
334	B24c	H	H	Cl	2-Cl	phenyl	c.C_6H_{11}-N(CH_3)-CH_2-	176°C
335	B13a	H	H	Cl	2-Cl	phenyl	$(CH_3)_2N$-$(CH_2)_2$-N(CH_3)-CO-CH_2-	132°C
336	B30b	H	H	Cl	2-Cl	phenyl	phenyl-CH_2-SO_2-NH-CH_2-	158°C
337	B13a	H	H	Cl	2-Cl	2,3-diF-phenyl	H	110°C

Table 4



Co. No.	Ex. No.	R^{4a}	R^{5a}	R^{11a}	R^{11b}	R^{11c}	Salt form / stereochemistry
338	B2a	H	H	OH	c.C_3H_5-CH_2-	CH_3	
339	B2a	H	H	H	C_2H_5O-CO-	OH	
340	B2a	H	Cl	H	H	H	
341	B2a	CF_3	Cl	H	H	H	
342	B2a	CF_3	Cl	phenyl	H	H	
343	B2a	H	H	H	H	NH_2	
344	B18	H	Cl	H	H	4-morpholinyl	CH_3SO_3H (1:1) H_2O (1:2)
345	B18	H	Cl	H	H	4-CH_3-1-piperazinyl	
346	B8b	H	Cl	H	H	H	(A); α^D_{20} = -346.46° (c = 6.35 mg/5 ml in CH_3OH)
347	B8b	H	Cl	H	H	H	(B); α^D_{20} = +326.15° (c = 6.73 mg/5 ml in CH_3OH)
348	B18	H	Cl	NH_2	H	H	
349	B23	H	Cl	H	H	4-morpholinyl	
350	B18	H	Cl	H	H	OH	
351	B18	H	Cl	H	H		

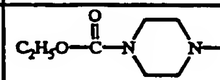
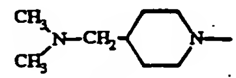
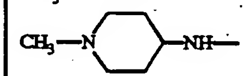
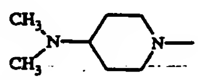
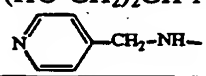
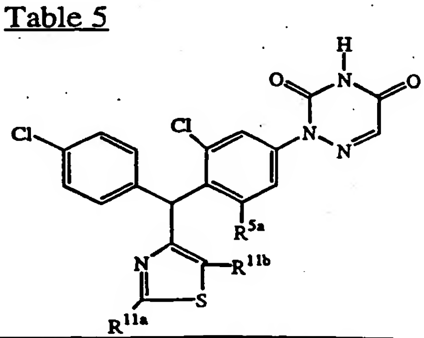
Co. No.	Ex. No.	R^{4a}	R^{5a}	R^{11a}	R^{11b}	R^{11c}	Salt form / stereochemistry
352	B18	H	Cl	H	H		
353	B18	H	Cl	H	H		
354	B18	H	Cl	H	H		HCl (1:1); H_2O (1:1)
355	B18	H	Cl	$(CH_3)_2$-N-	H	H	
356	B23a	H	Cl	H	H	CF_3-SO_2-O-	
357	B23b	H	Cl	H	H	HO-$(CH_2)_2$-NH-	
358	B23b	H	Cl	H	H	[HO-$(CH_2)_2$]$_2$N-	
359	B18	H	Cl		H	H	CH_3SO_3H (1:1)
360	B27	H	Cl	H	H	1-piperazinyl	H_2O (1:1)
361	B23	H	Cl	H	H	$(HO-CH_2)_2CH$-NH-	
362	B18	H	Cl	H	H		

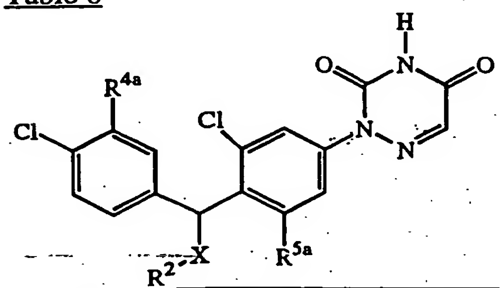
Table 5



Co. No.	Ex. No.	R^{5a}	R^{11a}	R^{11b}	Salt form / stereochemistry
363	B21	Cl	phenyl	H	
364	B21	Cl	2-F-phenyl	H	
365	B21	Cl	phenyl	CH_3-	
366	B21	Cl	4-pyridinyl	H	HCl (1:1); H_2O (1:1)
366a	B8a	Cl	4-pyridinyl	H	HCl (1:1); H_2O (1:1); (A)
366b	B8a	Cl	4-pyridinyl	H	HCl (1:1); H_2O (1:1); (B)
367	B21	Cl	2-Cl-phenyl	H	
368	B21	Cl	3-F-phenyl	H	
369	B21	H	CH_3	phenyl	
370	B21	Cl	3-F-phenyl	CH_3-	
371	B21	Cl	3-Cl-phenyl	H	

Co. No.	Ex. No.	R^{5a}	R^{11a}	R^{11b}	Salt form / stereochemistry
372	B21	Cl	3-CH_3-phenyl	H	
373	B21	H	phenyl	phenyl	
374	B21	Cl	2-CH_3-phenyl	H	
375	B21	Cl	3-pyridinyl	H	

Table 6

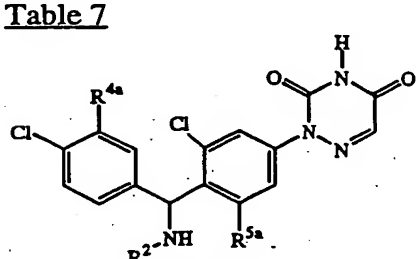


Co. No.	Ex. No.	X	R^2	R^{4a}	R^{5a}	salt form / stereochemistry melting point
52	B2a	S	1*H*-benzimidazol-2-yl	H	H	
53	B2a	S	4-CH_3-1,2,4-triazol-3-yl	H	H	
54	B2a	S	$(CH_3)_2N$-$(CH_2)_2$-	H	H	
55	B2a	S	1*H*-1,2,4-triazol-3-yl	H	H	
56	B2a	S	5-CH_3-1,3,4-thiadiazol-2-yl	H	H	
57	B2a	S	4-F-phenyl	H	H	
58	B2a	S	1-CH_3-2-imidazolyl	H	H	
59	B2a	S	4-aminophenyl	H	H	
60	B2a	S	4-OH-6-CH_3-2-pyrimidinyl	H	H	
61	B2a	S	4-OH-2-pyrimidinyl	H	H	H_2O (1:1)
62	B2a	S	5-CH_3-1*H*-benzimidazol-2-yl	H	H	
63	B2a	S	2-thiazolyl	H	H	
64	B2a	S	2-furanyl-CH_2-	H	H	
65	B2a	S	4-pyridinyl	H	H	
66	B2a	S	4,6-diCH_3-2-pyrimidinyl	H	H	
67	B2a	S	4-Cl-phenyl-CH_2-	H	H	
68	B2a	S	2,4-diamino-6-pyrimidinyl	H	H	
69	B2a	S	1*H*-purin-6-yl	H	H	
70	B2a	S	4,6-diamino-2-pyrimidinyl	H	H	
71	B2a	S	2-benzoxazolyl	H	H	
72	B2a	S	4-OH-6-propyl-2-pyrimidinyl	H	H	
73	B2a	S	2-pyridinyl, *N*-oxide	H	H	
74	B2a	S	1*H*-pyrazolo[3,4-d]pyrimidin-4-yl	H	H	
75	B2a	S	4-CH_3-2-pyrimidinyl	H	H	

Co. No.	Ex. No.	X	R^2	R^{4a}	R^{5a}	salt form / stereochemistry melting point
76	B2a	S	C_2H_5-O-C(=O)-CH_2-	H	H	
77	B2a	S	2-benzothiazolyl	H	H	
78	B2a	S	4,5-dihydro-2-thiazolyl	H	H	
79	B2a	S	4-(4-OCH_3-phenyl)-2-pyrimidinyl	H	H	
80	B2a	S	CH_3-O-C(=O)-$(CH_2)_2$-	H	H	
81	B2a	S	thiazolo[5,4-b]pyridin-2-yl	H	H	
82	B2a	S	4-OH-6-(CH_3OCH_2)-2-pyrimidinyl	H	H	
83	B2a	S	2-amino-1*H*-purin-4-yl	H	H	
84	B2a	S	4-(2-thienyl)-2-pyrimidinyl	H	H	
85	B2a	S	6-CH_3-5-oxo-4*H*-1,2,4-triazin-3-yl	H	H	
86	B2a	S	2-pyridinyl	CF_3	H	
87	B2a	S	4-amino-6-OH-2-pyrimidinyl	H	H	
88	B2a	S	5-CF_3-2-pyridinyl	H	H	
89	B2a	S	5-CF_3-4*H*-1,2,4-triazol-3-yl	H	H	
90	B2a	S	cyclohexyl	H	H	
91	B2a	S	5-ethyl-4-oxo-2(3*H*)-pyrimidinyl	H	H	
92	B1b	S	2-pyrimidinyl	H	H	
93	B2a	S	2-pyridinyl	H	H	
94	B2b	S	1*H*-imidazol-2-yl	H	H	
95	B2c	S	C_2H_5-O-C(=O)-CH(NH_2)-	H	H	
96	B11	S	2,4-diOCH_3-6-pyrimidinyl	H	H	
98	B1	O	CH_3	H	H	
133	B1	O	$(CH_3)_2$CH-CH_2	H	H	
376	B2a	S	thiazolo[5,4-b]pyridin-2-yl	H	Cl	
377	B2a	S	2-pyridinyl	H	Cl	
377a	B8a	S	2-pyridinyl	H	Cl	(A); α^{D}_{20} = +354.70° (c = 5.85 mg/5 ml in CH_3OH)
377b	B8a	S	2-pyridinyl	H	Cl	(B); α^{D}_{20} = -356.73° (c = 6.91 mg/5 ml in CH_3OH)
378	B2a	S	2-pyridinyl	CF_3	Cl	
379	B2a	S	2-benzoxazolyl	CF_3	Cl	
380	B2a	S	4-phenyl-2-thiazolyl	H	Cl	
381	B2a	S	4-phenyl-2-thiazolyl	CF_3	Cl	
382	B2a	S	thiazolo[5,4-b]pyridin-2-yl	CF_3	Cl	
383	B2a	S	2-benzoxazolyl	H	Cl	
384	B2a	S	2-benzothiazolyl	H	Cl	
385	B2a	S	2-benzothiazolyl	CF_3	Cl	

Co. No.	Ex. No.	X	R^2	R^{4a}	R^{5a}	salt form / stereochemistry melting point
386	B2a	S	4,5-dihydro-2-thiazolyl	CF_3	Cl	
387	B2a	S	2-thiazolyl	CF_3	Cl	
388	B2a	S	6-nitro-2-benzothiazolyl	CF_3	Cl	
389	B2a	S	6-NH_2-2-benzothiazolyl	CF_3	Cl	
390	B2a	S	4-(2-thienyl)-2-thiazolyl	CF_3	Cl	
391	B2a	S	5-phenyl-1,3,4-oxadiazol-2-yl	CF_3	Cl	
392	B2a	S	5CH_3-4-phenyl-2-thiazolyl	CF_3	Cl	
393	B2a	S	4-NH_2-phenyl	CF_3	Cl	
394	B2a	S	6-ethoxy-2-benzothiazolyl	CF_3	Cl	
395	B2a	S	pyrido[3,4-d]thiazol-2-yl	CF_3	Cl	
396	B2a	S	1*H*-benzimidazol-2-yl	CF_3	Cl	
397	B2a	S	4-(2,4-diF-phenyl)-2-thiazolyl	CF_3	Cl	
398	B2a	S	4-(CH_3-CO-NH)-phenyl	CF_3	Cl	
399	B2a	S	4-(2-furanyl)-2-thiazolyl	CF_3	Cl	
400	B2d	S	1,3-dihydro-4-phenyl-2*H*-imidazole-2-thion-5-yl	CF_3	Cl	
401	B2a	S	2-pyrazinyl	CF_3	Cl	
402	B2a	S	5-Cl-2-benzothiazolyl	CF_3	Cl	
403	B2a	S	pyrido[3,4-d]oxazol-2-yl	CF_3	Cl	
404	B2a	S	3-phenyl-1,2,4-oxadiazol-5-yl	CF_3	Cl	
405	B2a	S	5-CH_3-4-phenyl-2-thiazolyl	CF_3	Cl	
406	B18	S	5-phenyl-1,3,4-oxadiazol-2-yl	H	Cl	
407	B2a	S	(2-pyrazinyl)-CH_2-	H	Cl	216°C
408	B18	S	3-phenyl-1,2,4-oxadiazol-5-yl	H	Cl	
409	B18	S	4-pyrimidinyl	H	Cl	

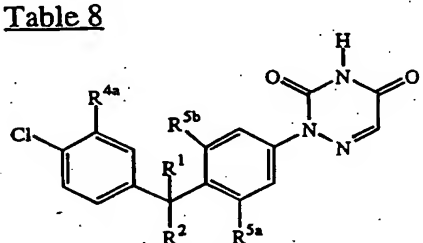
Table 7



Co. No.	Ex. No.	R^2	R^{4a}	R^{5a}	salt form
40	B3e	5-CH_3-3-isoxazolyl	H	H	
41	B3c	CH_3-O-$(CH_2)_2$-	H	H	
42	B3c	4-CH_3-6-OCH_3-2-pyrimidinyl	H	H	
43	B3c	2-furanylethyl	H	H	HCl (1:1)
44	B3c	2-thiazolyl	H	H	

Co. No.	Ex. No.	R^2	R^{4a}	R^{5a}	salt form
46	B3a	cyclohexyl	H	H	
47	B10b	benzoyl	H	H	
48	B3f	1-CH_3-4-piperidinyl	H	H	
49	B3e	2-pyrimidinyl	H	H	
50	B3d	1*H*-imidazol-2-yl	H	H	
51	B3c	C_2H_4OH	H	H	
410	B10b	thiazolo[5,4-b]pyridin-2-yl	H	H	
411	B3g	4-phenyl-2-thiazolyl	CF_3	Cl	
412	B3c	5-CH_3-4-phenyl-2-thiazolyl	H	H	
413	B3g	2-pyrimidinyl	H	Cl	

Table 8



Co. No.	Ex. No.	R^1	R^2	R^{4a}	R^{5a}	R^{5b}	Salt form melting point
45	B3a	H	$N(CH_3)_2$	H	Cl	H	
97	B3c	H	1,2,4-triazol-1-yl	H	Cl	H	
99	B3c	H	1,2,4-triazol-4-yl	H	Cl	H	
100	B3c	H	1*H*-imidazol-1-yl	H	Cl	H	
101	B8a	H	5-phenyl-1,3,4-oxadiazol-2-yl	H	Cl	H	
102	B8a	H	5-CH_3-1,3,4-oxadiazol-2-yl	H	Cl	H	
103	B8a	H	5-phenyl-2-oxazolyl	H	Cl	H	
104	B8a	CH_3	5-phenyl-1,3,4-oxadiazol-2-yl	H	Cl	H	
105	B8a	H	5-phenyl-2-oxazolyl	H	Cl	Cl	
106	B6	CH_3	3-phenyl-1,2,4-oxadiazol-5-yl	H	Cl	H	
107	B7	H	5-phenyl-1,2,4-oxadiazol-3-yl	H	Cl	H	
108	B5a	H	2-CH_3-1,2,4-triazol-3-yl	H	Cl	H	
109	B5a	H	1-CH_3-2-imidazolyl	H	Cl	Cl	164°C
110	B4a	OH	2-CH_3-1,2,4-triazol-3-yl	H	Cl	H	H_2O (1:1)
111	B4a	OH	2-benzothiazolyl	H	Cl	H	
112	B5a	H	4-pyridinyl	H	Cl	H	
113	B5a	H	4-pyridinyl	H	Cl	Cl	
114	B5a	H	2-pyridinyl	H	Cl	H	130°C
115	B5a	H	2-pyridinyl	H	Cl	Cl	205°C
116	B5a	H	3-pyridinyl	H	Cl	Cl	166°C
117	B4a	OH	3-pyridinyl	H	Cl	H	

Co. No.	Ex. No.	R^1	R^2	R^{4a}	R^{5a}	R^{5b}	Salt form melting point
118	B3a	H	4-CH_3-1-piperazinyl	H	Cl	H	
119	B3b	H	4-OH-1-piperidinyl	H	Cl	H	
120	B4a	OH	1-CH_3-2-imidazolyl	H	Cl	H	H_2O (1:1)
121	B4b	OH	3-CH_3-4-imidazolyl	H	Cl	H	H_2O (1:1)
122	B4c	OH	CN-CH_2-	H	Cl	Cl	
123	B5a	H	1-CH_3--2-imidazolyl	H	Cl	H	
124	B5b	H	3-pyridinyl	H	Cl	H	
125	B6	H	3-phenyl-1,2,4-oxadiazol-5-yl	H	Cl	H	
126	B7	H	5-CH_3-1,2,4-oxadiazol-3-yl	H	Cl	H	
127	B8a	H	5-phenyl-1,3,4-oxadiazol-2-yl	H	Cl	Cl	
128	B9	H	5-SH-4-phenyl-1,2,4-triazol-3-yl	H	Cl	H	
129	B9	H	5-(phenyl-NH)-1,3,4-thiadiazol-2-yl	H	Cl	H	
130	B12	H	2-benzothiazolyl	H	Cl	H	
131	B15a	H	2-benzoxazolyl	H	Cl	H	
132	B15b	CH_3	2-benzoxazolyl	H	Cl	H	240°C
414	B12	H	5-phenyl-1,3,4-thiadiazol-2-yl	H	H	Cl	128°C
415	B17a	Cl	2-benzothiazolyl	H	Cl	H	
416	B17b	NH_2	2-benzothiazolyl	H	Cl	H	140°C
417	B4c	HO	CN-CH_2-	CF_3	Cl	Cl	
418	B16	CH_3O	2-benzothiazolyl	H	Cl	H	100°C
419	B20	H	(4-phenyl-2-thiazolyl)-CH_2-	H	H	Cl	90°C
420	B19a	H	HO-CH_2-	H	Cl	Cl	
421	B5a	H	2-benzothiazolyl	H	Cl	Cl	208°C
422	B19c	H	(2-pyrimidinyl)thio-CH_2-	H	H	Cl	
423	B19a	H	HO-CH_2-	CF_3	Cl	Cl	
424	B19b	H	H_3C-SO_2-O-CH_2-	CF_3	Cl	Cl	
425	B5a	H	1-CH_3-4-phenyl-2-imidazolyl	H	Cl	Cl	>250°C
426	B8a	H	5-CH_3-4-phenyl-2-oxazolyl	H	Cl	Cl	150°C
427	B12	H	5-phenyl-1,3,4-thiadiazol-2-yl	H	Cl	Cl	140°C
428	B5a	H	4-CH_3-5-phenyl-1,2,4-triazol-3-yl	H	Cl	Cl	H_2O(1:1)/245°C
429	B6b	H	3-phenyl-1,2,4-oxadiazol-5-yl	H	Cl	Cl	128°C
430	B5a	H	1-CH_3-2-phenyl-5-imidazolyl	H	Cl	Cl	>260°C
431	B8a	H	5-CH_3-4-(4-F-phenyl)-2-oxazolyl	H	Cl	Cl	220°C
432	B21	H	5-phenylimidazo[2,1-b]thiazol-6-yl	H	H	Cl	
433	B21	H	5,6-dihydro-2-phenylimidazo-[2,1-b]thiazol-3-yl	H	H	Cl	
434	B5a	H	2,4-diphenyl-5-oxazolyl	H	Cl	Cl	195°C
435	B19b	H	H_3C-SO_2-O-CH_2-	H	Cl	Cl	

C. Pharmacological example

Example C.1 : *in vitro* inhibition of IL-5 production in human blood

Human whole blood stimulation

Peripheral blood from healthy male donors was drawn into heparinized syringes (12.5 U heparin/ml). Blood samples were three-fold diluted in RMPI 1640 medium (Life Technologies, Belgium) supplemented with 2 mM L-glutamine, 100 U/ml penicillin and 100 µg/ml streptomycin, and 300 µl fractions were distributed in 24-well multidisc plates. Blood samples were preincubated (60 minutes at 37°C) in a humidified 6% CO_2-atmosphere with 100 µl of drug solvent (final concentration 0.02% dimethylsulfoxide in RPMI 1640) or with 100 µl of an appropriate dose of test compound before being stimulated by the addition of 100 µl of phytohemagglutinin HA17 (Murex, UK) at a final concentration of 2 µg/ml. After 48 hours, cell-free supernatant fluids were collected by centrifugation and stored at -70°C until tested for the presence of IL-5.

IL-5 measurements

IL-5 measurements were conducted as described in Van Wauwe et al. (1996, Inflamm Res, *45*, 357-363) on page 358 using ELISA.

Table 9 lists the percentage inhibition of IL-5 production (column "% inh") at a test dose of 1 x 10^{-6} M, or in case the percentage inhibition is marked with an "*" 1 x 10^{-5} M, for the compounds of the present invention.

Table 9

Comp No	% inh.	Comp No	% inh.	Comp No	% inh.	Comp No	% inh.	Comp No	% inh.	Comp No	% inh.
1	77	18	88	37	61	55	26	74	69	95	17
2	55*	19	83	38	92	56	41	75	72	96	62
3	46	20	70	39	68	57	50	76	2	97	26
4	83	21	91	40	31	58	5	77	65	101	66
5	77	22	93	41	11	59	76	78	70	102	14
6	91	23	83	42	57	60	24*	79	74	103	63
7	95	24	74	43	37	61	14	81	76	104	60
8	93	25	88	44	40	62	30	82	19	105	88
9	85	26	85	46	64	63	68	84	73	106	77
10	64	27	64	47	33	64	64	85	38	107	81
11	91	28	73	48	29	65	50	86	84	109	35
12	77	29	95	49	61	66	64	87	9	110	6
13	61	30	57	50	20*	67	69	88	26	111	61
14	83	31	93	51	10	68	60	89	19	112	62
15	86	32	90	52	57*	70	51	90	60	113	76
16	89	34	58	53	53*	71	84	93	86	114	40
17	81	35	56	54	14	73	21	94	18	115	71

Comp No	% inh.
116	74
117	34
118	34
119	72*
120	10
123	13
124	42
125	52
126	40
127	94
130	70
131	76
132	55
133	50
134	95
135	88
136	93
137	64
138	81
139	60
140	45
141	64
142	80
143	81
144	40
145	37
146	83
147	50
148	79
149	89
150	48
151	17
152	87
153	72
154	42
155	80
156	91
157	85
158	92
159	87
160	91
161	91
162	63
163	90
164	84
165	80

Comp No	% inh.
166	87
167	82
168	80
169	81
170	62
171	59
172	17
173	44
174	83
175	58
176	3
177	69
178	78
179	21
180	54
181	55
182	75
184	83
185	81
186	8
187	25
188	95
189	82
190	83
191	19
194	83
195	7
196	35
198	46
199	43
200	43
201	87
203	82
204	36
205	80
206	82
207	94
208	48
209	77
210	79
211	83
213	32
215	54
218	4
219	8
220	25

Comp No	% inh.
221	-2
224	95
225	80
226	93
227	78
228	81
230	79
232	47
233	84
234	83
235	79
236	92
237	82
238	74
239	72
240	54
241	95
242	98
243	97
244	95
245	98
246	94
247	80
248	91
249	80
250	84
251	90
252	80
253	96
254	86
255	67
256	94
257	82
258	98
259	95
260	98
261	93
262	93
263	92
264	79
266	46
267	81
268	83
269	90
270	86
271	88

Comp No	% inh.
272	87
273	77
274	89
275	94
276	91
277	66
278	97
279	92
280	96
281	91
282	93
283	93
284	91
285	89
286	86
287	94
288	90
289	96
290	92
292	94
293	59
294	85
295	90
296	92
297	90
299	38
300	27
301	33
302	87
303	85
304	35
305	51
306	92
307	78
309	82
310	79
311	64
312	57
313	86
314	81
315	93
316	85
317	67
318	81
319	84
320	94

Comp No	% inh.
321	92
322	96
325	95
326	89
327	84
329	88
330	94
331	95
332	86
333	61
334	75
335	52
336	88
337	96
338	-15
339	35
340	88
341	96
342	93
343	66
344	82
345	88
346	86
347	8
348	83
349	87
351	62
352	85
353	91
354	70
355	83
357	69
358	63
359	88
360	84
361	28
363	91
364	95
365	88
366	93
367	74
368	88
369	66
370	76
371	88
372	86

Comp No	% inh.
373	40
374	94
375	91
376	92
377	87
378	91
379	95
380	95
381	95
382	95
383	78
384	95
385	95
386	97
387	93
388	90
389	91
390	89
391	97
392	87
393	93
394	93
395	94
396	28
397	83
398	96
399	93
400	76
401	92
402	90
403	97
404	92
405	80
406	84
407	71
408	88
409	88
410	15
411	94
412	16
413	59
414	30
416	79
418	47
419	5
420	33

Comp No	% inh.
421	86
422	87

Comp No	% inh.
425	70
426	92

Comp No	% inh.
427	72
428	66

Comp No	% inh.
429	78
430	89

Comp No	% inh.
431	67
432	82

Comp No	% inh.
433	53
434	72

D. Composition examples

The following formulations exemplify typical pharmaceutical compositions suitable for systemic or topical administration to animal and human subjects in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a pharmaceutically acceptable addition salt thereof.

Example D.1 : film-coated tablets

Preparation of tablet core

A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinyl-pyrrolidone (10 g) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline cellulose (100 g) and hydrogenated vegetable oil (15 g). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of methyl cellulose (10 g) in denaturated ethanol (75 ml) there was added a solution of ethyl cellulose (5 g) in CH_2Cl_2 (150 ml). Then there were added CH_2Cl_2 (75 ml) and 1,2,3-propanetriol (2.5 ml). Polyethylene glycol (10 g) was molten and dissolved in dichloromethane (75 ml). The latter solution was added to the former and then there were added magnesium octadecanoate (2.5 g), polyvinyl-pyrrolidone (5 g) and concentrated color suspension (30 ml) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example D.2 : 2% topical cream

To a solution of hydroxypropyl β-cyclodextrine (200 mg) in purified water is added A.I. (20 mg) while stirring. Hydrochloric acid is added until complete dissolution and next sodium hydroxide is added until pH 6.0. While stirring, glycerol (50 mg) and polysorbate 60 (35 mg) are added and the mixture is heated to 70°C. The resulting mixture is added to a mixture of mineral oil (100 mg), stearyl alcohol (20 mg), cetyl alcohol (20 mg), glycerol monostearate (20 mg) and sorbate 60 (15 mg) having a temperature of 70°C while mixing slowly. After cooling down to below 25°C, the rest of the purified water q.s. ad 1 g is added and the mixture is mixed to homogenous.